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MASTER THESIS

Absolute beta-1 power as an indication of synaptogenesis in children with Perinatal Arterial Ischaemic Stroke

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CONTENTS

Introduction……..4

Chapter 1 Brain development……..…….7
1.1. Overview…….7
1.2. Gestational Period……...7
1.3. Postnatal Period……...8
1.4. Cognitive and Motor Development…….9
1.4.1. Motor Development……...10
1.4.2. Cognitive and Language Development……..11
1.5. PFC and Higher Cognitive Functions……..12
Chapter 2 Neuroplasticity…….……14
2.1. Overview……..14
2.2. Neurogenesis……15
2.3. Synaptic Placticity……16
2.4. The Role of GABA in Neuroplasticity…….18
2.4.1. GABA's Functions and the Balance Between Excitation and Inhibition…….18
2.4.2. GABA's Role in Development……20
2.4.3. GABA's Role in Disease…….……21
Chapter 3 Reorganization After a Lesion……...……24
3.1. Overview……...24
3.2. Location, Timing and Size of Perinatal Lesion…….25
3.3. Neural Plasticity or Neural Vulnerability……..26
3.3.1. Sensorimotor Plasticity……26
3.3.2. Visual Plasticity……28
3.3.3. Language Plasticity……..28
3.3.4. Cognitive Plasticity……..……....29
Chapter 4. Perinatal Arterial Ischemic Str……..30
4.1. Overview……...30
4.2. Outcomes……...32
4.2.1. Motor Deficits...……...32
4.2.2. Cognitive Deficits……32
4.2.3. Language Deficits……34
4.2.4. Visuospatial Deficits……34
4.2.5. Somatosensory Deficits……35
4.2.6. Epilepsy……35
4.3. Neuroimaging Methods for Diagnosis……..36
4.4. Motor and Non-Motor Rehabilitation……..……..37
Chapter 5 Neuroimaging for Synaptogenesis ...……..39
5.1. Overview……39
5.2. EEG Use In Infants……39

5.2.1. The Development of EEG in Infants and Children……...40
5.3. Different EEG band and Neuroplasticity……41
5.3.1. Beta-Band and Functions…...……41
Method……45
Results……..56
Conclusion……73
References……78

INTRODUCTION

Perinatal Arterial Ischemic Stroke (PAIS) is a fairly common cerebrovascular disease associated with long term neurological impairment [154]. It damages the immature brain causing motor and non-motor problems [62]. The lesion activates recovery mechanisms in the ipsilesional and/or contralesional hemisphere, with synaptogenesis lasting as long as a few months after the incidence [30, 141]. However, brain reorganization isn't always adaptive with contralesional reorganization being connected with adverse motor outcome.

Regarding motor consequences, PAIS is a major cause of cerebral palsy while the non-motor consequences, such as cognitive, can be more difficult to study as they often emerge later [23]. It has been reported an early vulnerability of the Prefrontal Cortex (PFC), a brain area which supports Higher Cognitive Functions, due to its prolonged development with its first synaptogenetic peak being reached after the first year of life [126, 160, 54].

This raises the issue if the young brain is indeed more effective in overcoming an injury or is more vulnerable, especially the area of PFC, with two conflicting theories describing this two suggestions; neural plasticity (Kennard principle) and neural vulnerability [60, 160].

Several scientific methods such as fMRI have been used in the past to investigate neuroplasticity. During last years there is an increasing scientific interest in EEG, a non-invasive neuroimaging method with better temporal resolution (milliseconds) than fMRI, less expensive and more applicable to infants and young children. Recent progress in the knowledge of EEG bands and their association with different psychological functions led many scientists to use this method to study neuroplasticity [178]. However, there is still a lot of debate, due to inconsistent data, about the specific role of EEG bands in different psychological functions.

A recent study associated positively absolute beta-1 power with synaptogenesis, ergo relating GABA-ergic system with the latter as beta power is considered the pacemaker of GABA-ergic interneurons [21]. What they found was that 5months but not 10months preterm infants had lower absolute beta-1 power than the corresponding typical group, indicating physiological differences in the timing of their brain maturation.

The scientific goals of this study are three-fold. The first is to gain more knowledge about the characteristics and mechanisms of the early neuroplasticity and the young brain's higher or compromised capacity to reorganize its affected neural connections and overcoming the neurological problems. The second is to find faster and more efficient ways to measure (directly or indirectly) synaptogenesis during wakefulness by learning more about the role of beta-band, one of the longest EEG bands. And the third goal is to contribute to the creation of more effective therapeutic interventions for young children who have endured PAIS, which dwells from the need of a more preventative approach as up till now the interventions and therapeutic programs have been built once the symptoms have emerged.

So, the importance of this study lies not only on the expansion of the knowledge about early neuroplasticity and the beta-band but also by establishing absolute beta-1 power as a biomarker of synaptogenesis, understanding on time the severity and extent of the lesion, forming an early intervention and preventing any potential adverse outcome such as motor or cognitive, especially the latter as it is usually masked during the early stages.

The object of the study is synaptogenesis in the young healthy and lesioned brain. The subject of the study is the relation of synaptogenesis with absolute beta-1 power and the level of motor and cognitive development.

The first hypothesis is that absolute beta-1 power of children with PAIS, is more interhemispheric asymmetric, in comparison with typical children. The second hypothesis is that higher contralesional beta-1 power is associated with

lower Motor Raw Scores on Bayley-III test. The third hypothesis is that the 24month PAIS subgroup will have lower absolute beta-1 power in the PFC and lower Cognitive Raw Scores than the Typical Group. The fourth hypothesis is that the the 5month, 10month and 24month PAIS subgroups will have lower absolute beta-1 power in the Premotor and Sensorimotor Cortices and lower Motor Raw Scores than the Typical Group.

Several tools were used for the data collection. First via EEG the background activity of the children was measured, focusing on beta-1 power while NetStation 4.6.3. software was used to analyze the EEG data. Then Bayley-III test was used to assess the neurodevelopmental status of the sample. The analysis of the data and the interpretation of the results were achieved by using quantitative non-parametric Mann-Whitney U-test and Kruskal Wallis H-test and were based on the theoretical background in the first part of the study.

The thesis begins with the first chapter describing brain development from uterus to postnatal period and the development of child's abilities including motor, cognitive functions. The second chapter continues with the description of neuroplasticity, its types and mechanisms while the third chapter depicts the role of GABA-ergic system in neuroplastic processes. The fourth chapter discusses the neuroplastic processes and brain reorganization which take place after a lesion, focusing on perinatal lesion, and how these processes depend on factors such as lesion location and lesion timing. The fifth chapter describes PAIS, its outcomes, the methods for diagnosis and rehabilitation. The sixth chapter concludes with the depiction of measures for synaptogenesis, the potential association of beta band with synatogenesis and the link between between beta band and GABA interneurons' activity. The Method chapter discusses the participants, the materials and the procedure. The Results chapter analyzes the collected data and answers the correctness of the hypotheses. Lastly the Discussion chapter interprets the results linking them back to theory and describes the study's limitations along with proposals for future studies.

1. BRAIN DEVELOPMENT

1.1. OVERVIEW

Brain development is a long lasting process starting from uterus till the early adolescence with different core procedures (neurogenesis, synaptogenesis, pruning) dominating at each stage and with different brain regions reaching full maturity at different times influencing the child's abilities [172, 115]. The biggest part of neurogenesis, neural migration and differentiation takes part during gestational period whereas synaptogenesis occurs mostly during postnatally. Both genetic and environmental factors are major contributors in this whole process. This complex organ will eventually become the mediator of human cognition, behavior and emotions.

1.2. GESTATIONAL PERIOD

The human brain takes its broad form during the first 6 months after conception with development following a caudal to rostral trajectory [115, 54].

During the third gestational week [172] the neural plate, originating from the ectoderm and one of the three germ layers, starts to fold and becomes the neural tube, a process known as neurulation [180]. Eventually it differentiates to the forebrain, the midbrain, the hindbrain and the spinal cord. Towards the walls of the neural tube, lie the progenitor cells (or stem cells) [54] which through mitosis give birth to other stem cells or neuroblasts (precursor of neurons) creating the proliferative zones; the ventricular and subventricular zone. These neural precursors go through the stages of migration towards the cortical plate, differentiation and ultimately axonal and dendritic growth.

Before the baby is born its brain has undergone neural cell death by almost 50% as a part of the normal development [162]. Around 26^{th} and 36^{th} gestational

week the young brain resembles the adult brain wit its six cortical layers [115]. Motor and sensory cortices are one of the first areas to appear [54].

1.3. POSTNATAL PERIOD

As the most part of neurogenesis and neural migration has already occurred, the proliferating zones decrease to the subpendumal zone which now gives birth mainly to glial cells for the whole brain and some neurons (in lesser extent than prenatally) to the frontal areas [116]. This area, along with the dentate gyrus in the hippocampus are the only two ongoing proliferating zones of the young and adult brain. However their neural contribution is quite small [162].

Synaptogenesis, myelination, increase of brain metabolism and neurotransmitters, and pruning are the major processes that shape the structure and function of the postnatal brain [54]. Their general trajectory follows a sudden increase, reaching higher levels than adults and then slowly decreasing back to adult levels [162]. However these processes have different timings based on location, with the Primary Sensory and Motor areas maturing earlier than Associative areas [54]. Synaptogenesis in the Visual and Auditory Cortex peaks around the third and forth month and by the end of the first year the overall density has reached 150% of the adult level. In contrast a rapid burst of synapses in PFC is seen after the first year of life. Myelination refers to the production of the protected lipid-sheath around the neural axons to support effective inter-neural communication [175]. As before, the sensorimotor regions are the first to myelinate during mostly the first two years, with sensory areas being the very first whereas association regions myelinate last with PFC persisting to do so until the second decade [54, 172]. MRI studies have shown that myelinating measures continue to persist throughout life revealing the ongoing process of learning [54].

Intrinsic gamma aminobutyric acid (GABA) emerges first and increases rapidly during the first few weeks of postnatal life followed by a decrease.

Glutamate follows a similar pattern during the first postnatal weeks although with slight delay than GABA. The rest of the extrinsic neurotransmitters such as achetylocholine, serotonine, norepinephrine and dopamine start to develop prenatally from subcortical to cortical areas reaching adult levels by 10 years of age. Increase of glucose and brain metabolism starts after the first year of live, peaking around 4-5 years of age and then decreases.

Pruning is an important stage of brain development and it refers to the fine-tuning of synapses, making the neural inter-connections more effective with less spent brain energy. It is related to the establishment of neural networks with the environmental input contributing to the synaptic persistence and optimization, while synapses which are not used perish. It starts prenatally and then after the postnatal growth peak it eliminates synapses first in the Primary Areas and lastly in PFC and continues, in the latter area, until the beginning of the third decade.

1.4. COGNITIVE AND MOTOR DEVELOPMENT

Early brain development sets the foundation for acquiring abilities such as language, abstract thinking, voluntary movement [168] while the environmental contribution is paramount. Motor, cognitive and social development are believed to be interrelated [47, 72] with Piaget emphasizing how a child learns as it moves and manipulates objects [145] while recent studies continue to verify this view [129, 167].

In 1936, Piaget (1896-1980) studied the cognitive development of children and developed his theory. He described four different stages; sensorimotor, preoperational, concrete operational and formal operational [145].

The Sensorimotor stage starts from birth till 2 years of age where the cognitive development is mostly driven by the sensorimotor areas and language doesn’t play a particular role. During that time the child is characterized by a sensory curiosity and it coordinates its senses with its motor responses. Also, by

the end of the second year of life the child fully gains object permanence and can successfully find a hidden object.

The Preoperational stage is between 2 and 7 years of age and at this point cognitive development is driven by linguistics. Children start to have symbolic thinking and to use their imagination. They begin to have conversation as they learn syntactical and grammar rules although their complex abstract thought is still immature.

During the Concrete Operational stage which takes place between 7 and 11 years of age, the child develops concepts attached to concrete situations. They are able to understand and use concepts such as time, space, quantity.

Lastly, a child from 11 years of age and onwards enter the Formal Operational stage developing their theoretical, hypothetical and counterfactual thinking. They start to show abstract logic and reasoning, use strategies and planning and generalize their concept knowledge.

1.4.1. MOTOR DEVELOPMENT

During the first 5 years the child achieves most of his Gross Motor milestones with the Fine Motor development continuing its fine-tuning in later stages [47]. Motor development involves the proper functioning and myelination of motor and sensory neurons which as it has been mentioned, it’s mostly finished around the second year. Also the development of cerebellar tracts is important to achieve proprioception which mainly serves the fine motor skills.

An infant is born with all its primitive reflexes such as grasping, rooting, in flexed position and unable to lift his head. By 4 months it’s able to lift its head, and the primitive reflexes have already began to diminish due to the cortical development. The infant is able to grasp and drop objects. At 8 months it can crawl, roll over, sit straight without support and walk with assistance. When it reaches its first year it can stand, turn pages on a book while 4 months later it can

walk, run, crawl up stairs. By 2 years, as the cerebellum function and its coordination have been improved, the child can jump. And at 3 years it can descend the stairs properly, draw a circle and acquires its handedness.

A pediatrician assess the ability of the child to reach these milestones and a delay is confirmed if two or three months have passed without achieving the milestones.

1.4.2. COGNITIVE AND LANGUAGE DEVELOPMENT

A newborn's vision is highly limited (20-30 cm) permitting only breastfeeding. Although it reacts to voice it doesn't recognize the words. Studies have indicated the preference for human faces from the first few months as the infant establishes eye contact [33, 54, 158]. At 2 months, the infant is able to differentiate between patterns, colors and consonants [47]. It can track an object horizontally at 180° (midline). A couple months later it can notice the objects crossing the midline and starts to explore more its surroundings, recognize emotions and mirror the facial expressions. At 6 months, it starts learning about cause and effect while dropping objects. By 9 months object permanence has reached an important stepping stone and the infant can uncover hidden objects although with still some limitations [146]. It recognizes and respond to its name and starts babbling saying "mama" or "dada" [47].

In the first year the child's cognition increases even further as the child begins to walk and navigate himself away from its caregivers. It is able to identify a word other than mama or dada and can follow one step command ("come here", "give me that"). Six months later it has learned 10 words and can understand the word "no" which sets the foundation for following rules and to adapt its behavior appropriately.

By 2 years its vocabulary has reached 50-100 words and can put a sentence together. There is a dramatic shift in the child's cognition due to the fact that it

starts using verbs which, in contrast to nouns, have more symbolic quality. At 3 years of age the child is aware of its age and gender, it can count at least till 3 and name at least 3 colors, say its name when asked and use personal pronouns correctly. One year after it obtains the ability to use past tense enabling it to narrate an experience or a story revealing their language and memory development. By this age magical thought dominates and the imaginary friends may exist or fear of the monsters underneath the bed.

1.5. PFC AND HIGHER COGNITIVE FUNCTIONS

PFC has been traditionally associated with the higher cognitive functions such as decision-making, planning, emotional processing and language [126, 54, 144]. It shows a protracted developmental period compared to the rest of the brain areas and its complex structure along with its extensive network are giving him an important role in cognitive and motor development. In fact Johnson [54] described the important role of PFC in learning due to its wide network as it is able to organize and allocate information within the same or other brain regions promoting the process of cortical plasticity and acting as structure with the highest control.

The prefrontal areas have bidirectional connections with the anterior and posterior regions from both hemispheres and the subcortical regions. Particularly it receives and sends information from the Sensory Association areas and indirectly from the Primary Sensory Cortices (visual cortex, auditory cortex, somatosensory cortex), from the thalamus (mainly with the mediodorsal nucleus) and the limbic system, inter-relating the cognitive and emotional aspects of a task [126, 172, 5].

PFC is comprised by 13 areas in Broadman’s map [173, 5] with the lateral PFC (LPFC), medial PFC and orbitofrontal being the 3 main ones. The lateral areas are associated with executive functions such as working memory; selection, retrieval, comparison and judgment of information kept in short-term and long-term memory. In its inferior part lies Broca’s areas, responsible for language

production. These regions form connections with the thalamus, hippocampus, orbitofrontal cortex, basal ganglia, Primary and Secondary Association areas (posterior temporal, parietal, occipital areas). The posterior part of the medial and orbital areas communicate with the limbic system participating in the reward system, the motivational/emotional value of a certain stimulus, empathy and social appropriate behavior. The lateral part of the orbital cortex forms the so-called frontostriatal circuit which communicates with the basal ganglia and the Premotor Cortex.

Luria [126] considered PFC as the cortical ending of the motor analyzer and its connections with motor areas, such as premotor and motor cortices, render it the base of the higher motor behavior: Goal-Directed Behavior. Generally PFC has efferent and afferent connections with the basal ganglia and cerebellum (mainly through thalamus) [5]. The LPFC is connected with the Premotor cortex and through that the Primary Motor Cortex implicating it with behavior. The Frontal Eye Fields, responsible for the orientation reflex towards a stimuli is connected with the superior colliculus. The connections of the Medial and Orbital PFC with hypothalamus, brain stem and through these with the internal organs (heart, lungs, gut) implicate them with emotional processing and expression.

Lesions to the LPFC is associated more with executive function disturbances such as inability to ignore irrelevant/unessential stimuli seen in Frontal Syndrome or schizophrenia whereas the Medial and Orbital PFC is associated more with emotional and social behavioral disturbances similarly to a lesion in the limbic system such as Anxiety Disorders and Obsessive Compulsive Disorder.

2. NEUROPLASTICITY

2.1. OVERVIEW

Plasticity refers to the life-long capacity of the brain to change the structural and functional organization of its neural circuits in order to continuously adapt to the environment, aging and potential injury [174, 130]. These changes can be observed on a small-scale on the properties of a single neuron and at a large-scale on the broad neural networks and brain architecture [99]. Also plasticity can be divided as short-term or long-term plasticity [37].

During the previous century Santiago Ramón y Cajal (1852-1934) depicted the cerebral gymnastics hypothesis describing a normal alteration of the brain architecture due to the addition of new connections [130]. This new preposition contributed to the change of the previous status quo which described the stability of the brain and the unchangeable number of its neurons. However it was William James (1842–1910) who first proposed the term “neuroplasticity” describing the ongoing ability of the brain to functionally alter itself [53]. The famous quote “What fires together, wires together” outlines Hebb’s theory (1904-1985) regarding synaptic plasticity, learning and memory. It was initially introduced in his book in 1949 “Organization of behavior” [45]. It delineates the strengthening of the axon-dendrite connection between two neurons when the presynaptic neuron fires just before the presynaptic neuron, leading to the pruning of the connections which didn’t fulfill these criteria.

In 1999 Grafman and Litvan [40] categorized brain plasticity into four types; homologous area adaptation, cross-modal reassignment, map expansion, and compensatory masquerade. The first one refers to the capacity of the brain to “transfer” a particular function to the homologous region of the other hemisphere. The second one is related to the capacity of a brain region, which is dedicated to a specific sensory stimulus, to “accept” a new sensory stimulus. The third one is

when a certain functional region expands based on training. Lastly, the fourth one refers to the capacity of a certain function to change brain location.

Recent studies have been dividing neuroplasticity to structural and functional plasticity [22] including phenomenons such as addition of new neurons (neurogenesis), new synapses (synaptogenesis) and biochemical changes. Structural plasticity refers to neurogenesis, neural migration and synaptic plasticity. The first two occur during development (developmental plasticity), neural death in cases of brain injury and the third occurs throughout life involving changes in density of white and gray matter as observed in MRI. Functional plasticity refers to phenomenons such as learning and memory, involving structural and biochemical changes within and outside the neuron that lead to enduring alterations in neural connections.

2.2. NEUROGENESIS

Although the major part of neurogenesis occurs during prenatal brain development, with few addition postnatally in the frontal lobe [162], recent studies have revealed neurogenetic processes in the adult animals and humans, with novel neuroblasts being generated from stem cells in the limbic system and basal ganglia [22, 56]. Adult neurogenesis remains an ambiguous subject regarding the exact mechanisms that are involved in the process, the course of life of neuroblasts, and how the novel neurons will be integrated in brain function.

In the middle of the last century, two scientists, Joseph Altman (1925-2016) and Gopal Das (1933-1991) challenged the scientific view that saw neurogenesis taking place only prenatally by showing that the hippocampal undifferentiated neurons of rats continued their mitotic processes even after birth [56] .

Today, the scientific world acknowledges two brain areas which are involved in adult neurogenesis; the dentate gyrus of hippocampus (particularly the subgranular zone- SGZ) and subventricular zone (SVZ) [56]. In these areas, stem

cells undergo mitosis, generating neuroblasts, which then migrate and generate more neurons [54]. According to Spalding and his team [109], 700 novel neurons are born in each hippocampus every day of a human's life with a moderate decreasing rate with aging. New neurons have been found in cortex, amygdala, hypothalamus and striatum regions [56, 57]. Some studies have linked neurogenesis with several functions and behaviors such as pattern separation, mood, social adaptation, sense of smell, learning and memory [181, 39].

Although stem cells exist in great numbers inside the brain, only a small amount of them will eventually be added in the circuit of hippocampus [109]. Various studies have attempted to shed light on the mechanisms which influence the process of neurogenesis. Kandasamy and Aigner [56] proposed three types of neuroblasts (housekeeping, neurogenic, intermediary or immunogenic) which may be influenced in a different way from the effects of extrinsic or intrinsic factors such as learning, sensorimotor stimuli, disease and therapy.

An enriched environment can promote the life-sustenance of neurons and integration of novel neurons on hippocampal circuit by influencing the activity of neurotrasmitters. Abnormality or alteration in the process of neurogenesis (mainly in hippocampus) is associated with aging, chronic stress, drug abuse and early stages of diseases such as stroke, epilepsy, Alzheimer, Huntington, Parkinson, Amyotrophic Lateral Sclerosis, brain injuries and mood disorders.

2.3. SYNAPTIC PLASTICITY

Synaptic plasticity is considered the neurochemical basis of learning and memory with the synaptic effectiveness altering, depending on the synaptic "use" (activity-dependent synaptic plasticity) within a neural network [45, 130]. Hebb referred to the synaptic plasticity as "some growth process or metabolic change'' in the neuron [45].

The theory of Hebbian learning proposes three stages which include changes of synapses, the creation of “cell assembly” and “phase sequence”. Cells assemblies refer to a large group of interconnected neurons which can be activated at the same time multiple times by a stimulus, creating a “phase sequence”. The more often the neural group is activated together the more the synaptic connections between them become stronger [151]. This process provides the basis of cognitive function and potentially learning and memory.

Long Term Potentiation (LTP) and Long Term Depression (LTD) regulate synaptic efficacy and signal transmission by increasing or decreasing synaptic strength based on the previous electric activity, leading to persistent changes of the neural cell morphology and activity such as the amount of neurotransmitters which are released in the synaptic cleft, the glutamergic receptors of the post-synaptic neuron, the neuromodulators, the signaling pathways on the surface or inside of the neuron and also changes of gene expression and protein synthesis [164].

Many scientists have made a separation between synaptic and non-synaptic plasticity due to the fact that the above processes don’t always involve just alteration of the synapses. Although they are inter-related and both associated with memory, the latter refers to changes of the ion channels (resting and voltage-dependent channels and ion pumps) in the dendrite or the axon of the neuron, by the excitatory post-synaptic potential (EPSP) or the inhibitory post-synaptic potential (IPSP), leading to changes in its intrinsic excitability [133].

Examples of activity-dependent synaptic plasticity can be the fined-tuning of a child’s connections based on the language of their caregivers [68], the muscle development after ongoing physical exercise [164] or increase of the neural connection between auditory and motor cortex after practicing a musical instrument [179] .

So neuroplasticity refers to various types of changes in the brain which will eventually influence the individual activity and performance.

2.4. THE ROLE OF GABA IN NEUROPLASTICITY

Gamma-aminobutyric acid (GABA) was first discovered during the middle of the previous century [35] and it constitutes the main neurotrasmitter with inhibitory action in the central nervous system (CNS) of the developed mammalian brain and is responsible for 10%- 25% of the total number of neurons in the cortex depending on the cortical area (mostly in hippocampus and neocortex) [117, 55]. These neurons convey neural signals locally as they have small axons in comparison with the excitatory principal neurons [52] and are associated with neuroplasticity, sensory stimulus transmission, movement, attention and memory [42, 30].

It has three known types of receptors; GABA-A, GABA-B and GABA-C. The A and C receptors are ionotropic (ligand-gated ion channel) allowing chloride (Cl^-) to enter the post-synaptic cell membrane and has a fast inhibitory or hyperpolarizing effect in mature and non-pathological brain [35]. In contrast receptor B is metabotropic (G-protein coupled receptor) and has a slower inhibitory effect via permitting potassium (K^+) to flow through the cell membrane or thwarting the release of calcium (Ca^+) in the presynaptic axon terminal [117] .

Inhibition induced by GABA is divided in tonic and phasic inhibition [30, 121]. Extra-synaptic GABA-A receptors are responsible for the former and synaptic GABA-A receptors for the latter. Although the way they influence each other is still ambiguous, with a study in 2013 [121] showing that a rise of tonic inhibition was linked with a considerable fall of the phasic inhibition.

2.4.1. GABA'S FUNCTIONS AND THE BALANCE BETWEEN EXCITATION AND INHIBITION

Inside the brain, excitatory (glutamate) and inhibitory (GABA) forces don't just compete one another by sending opposite signals onto neural cells but they

work in a dynamic inseparable way, making GABA and glutamate activity, responsible for the proper formation of distinct neural networks and “cell assemblies” via a segregation mechanism [55]. Together the excitatory and inhibitory signals create circuit oscillations which coordinates in time and space the information transmission by the principal cells. This process would be impossible by the excitatory or inhibitory activity alone as the excessive excitatory activity could lead to an epileptic episode whereas an excessive inhibitory activity would lead to little communication between brain areas and coma [34, 52].

The back and forth communication between GABAergic interneurons and local excitatory principal cells form the feed-back inhibitory circuits while the inter-communication between GABAergic interneurons and far-distant excitatory neurons (e.g. subcortical regions, other cortical layers) form the feed-forward inhibitory circuits [52]. These two circuits are crucial in structuring the different cortical regions.

A rise in brain activity leads the glutamergic neurons to excite the GABAergic inteneurons and boost inhibition. Both excitation and inhibition decrease and increase simultaneously. Also, Turrigiano and his team [171] showed that a disruption of their inter-correlation will generate compensation mechanisms.

The collaborative activity between these two different “forces” is apparent in sensory inputs including somatosensory, auditory, olfactory and visual [50, 49, 80, 125, 43, 122] and in spontaneous cortical activity (resting-state brain circuits) [46, 142]. For example, researchers detected a rise in excitation after a short auditory tone which two milliseconds later was followed by an increase in inhibition [124]. Similar results were found also when the sensory stimulus was visual (light flash) [122]. These processes are mediated by the feed-back and feed-forward inhibitory circuits.

In relation to spontaneous brain activity during resting state (default dorsal attention, ventral attention, vision, auditory, somatomotor and frontopariaetal network) it has been hypothesized by various researchers that the detected low

local cortical activity and high long-range excitatory activity is mediated by the regulating role of feedback inhibitory circuit and the E/I balance [46].

Thus, the balance between excitation and inhibition (E/I balance) have crucial role in the functional processes of the brain.

The role of GABA in the mature human brain remains unclear with fewer studies than in animals, depending on the specific function.

Although the boosting of GABAergic activity with drugs such as benzodiazepines and barbiturates is negatively associated with memory, motor learning, more recent studies have revealed a more positive effect of GABA [120]. In 2019, Kim and his team [74], found that the decreased levels of GABA in the area of PFC of boxers who have sustained Traumatic Brain Injury is connected with worse memory, revealing the role of GABA as a potential marker of memory impairment. Another study in 2020 demonstrated that increased initial levels of GABA in hippocampus is associated with better retrieval performance and associative learning [120]. High GABA activity in Sensorimotor Cortex is also positively linked with sensory discrimination [152].

2.4.2. GABA'S ROLE IN DEVELOPMENT

GABAergic activity can be recorded in the animal brain in greater scale than excitatory activity during the late postnatal period [70] due to separate emergence timings. The neural effects of GABA during the early (embryonic and early postanatal period) and adult (in SVZ and SGZ) neurogenesis is different than its regular neuronal effects in the developed healthy brain [24, 35]

It was first described by Ben-Ari and his team in 1989 [38] that GABA has an opposite effect, than its usual, on post-synaptic immature neurons as it depolarizes them, instead of hyperpolarizing them, probably due to the increased level of the transporter NKCC1, responsible for the Cl^- inflow across the neuronal cell membrane in contrast with the transporter KCC2, responsible for the Cl^-

outflow. As the latter increases, GABA takes on its hyperpolarizng characteristic [70, 8].

Recent studies have verified the depolarizing effect of GABA finding evidence that it provokes Ca^{+} influx into the immature neurons [118, 106]. However this scientific view doesn't exist without its counter arguments [173].

Due to its initial depolarizing activity, it assumes a crucial part in the maturation process of the cortex and in the neurogenetic phases [70, 35] such as proliferation of neural precursors, migration and neuroblast differentiation, synaptic growth and synchronization of developing networks. Also GABA assists migration of both excitatory and inhibitory neurons. This effect on novel neurons can last 2-3 weeks from their birth.

In 2016, Oh and his colleagues [106] found that in the early developing mouse cortex, GABA transmission in the 2/3 cortical layer influences the generation of inhibitory and excitatory synapses and the "building" of the neural networks. Inducing blocking of GABA led to a synaptogenesis reduction in the 2/3 cortical layer. Also other studies demonstrated the GABA participation in the early period of plasticity in the visual cortex while it elongates this process [24].

The development of the hyperpolarizing GABA system signals the cortical maturity by concluding the critical period in which plasticity peaks leading to the decreasing of cell proliferation and migration and later to the emergence of faster frequencies [70, 24]. Thus hyperpolarizing GABA influences the distinct architecture and function of interneurons in the different cortical layers.

2.4.3. GABA'S ROLE IN DISEASES

The role of GABA in diseases may be polymorphous depending if it is synaptic (phasic inhibition) or extrasynaptic (tonic inhibition) [30]. Most of the studies focus on animals or adults who have sustained an ischemic stroke and are during the acute period.

Irregular high GABA activity during early brain development is connected disruption of plasticity and diseases including Rett syndrome, Down syndrome, schizophrenia and autism (now autistic spectrum disorder) [10]. Some researchers have indicated that GABA may have depolarizing effect in pathological circumstances including epilepsy [8, 14] . However, whether this phenomenon has beneficial or adverse effects on brain recovery is still on debate. Regarding the positive effects, it has been proposed that after a neuronal lesion, KCC2 decreases in order to reduce the spent energy which is needed to maintain Cl^- at low levels inside the cell and thus altering GABA's hyperpolarizing activity. Other researchers have hypothesized that after stroke, neurogenesis is induced from SVZ and GABA may has the same depolarizing effect as it does during neurodevelopment [35].

The link between reduction of GABA's release and motor recovery stroke has been established in several human but mainly animal studies describing that a decrease of inhibition during learning of a motor task in the Primary Motor Cortex after a stroke signals the increase of the excitability of the lesioned area and the process of motor plasticity [31, 87]. Clarkson and his team [82] specified these results to the tonic inhibition of GABA. However the reduction in GABAergic inhibition was not observed during a task which did not required learning or during resting-state [87].

The role of phasic inhibition is less understood although there are studies which suggest its potential benefits during stroke recovery [11, 30]. Phasic GABA is considered a neuroprotective factor, preventing neural cell death from excitotoxity during the acute period after stroke. In a rodent study, Hiu and his colleagues [30] detected that during recovery there is an increase of phasic inhibitory neural transmission in the cortex of mouses and increased effectiveness of GABAergic spontaneous activity in the pyramidal neural cells of cortical layer five (level of major cortical output towards subcortical areas and spinal cord) in contrast with the decrease of tonic GABA in the two association layers. Particularly they found that this increase was focused in the perilesional area and

later became more limited on layer five. Administration of zolpidem, a positive allosteric modulator, boosts the phasic activity of GABA was associated with positive behavioral outcomes.

In conclusion, the role of GABA in the brain is more than a stop-signal, taking part, with its depolarizing and hyperpolarizing function, to the shaping of neural networks, to brain plasticity such as synaptogenesis, to brain’s functions including sensory functions or memory and signaling the brain maturation.

3. REORGANIZATION AFTER A LESION

3.1. OVERVIEW

Human brain plasticity is an ongoing phenomenon, occurring everyday when acquiring new information or after an injury [174]. Our knowledge about the neural mechanisms that takes place after brain injury mainly comes from animal studies and adults that have suffered a stroke or a trauma. Recently there have been more studies investigating brain reorganization after an early lesion

Following a brain injury, the neural circuits in the lesioned hemisphere are changed, with researchers reporting an increase of delta or theta EEG power (slowing-wave activity) and decrease of faster frequencies in both hemispheres, mainly during the first 72 hours which suggest a disturbance in brain networks [104, 94, 165].

The brain activates mechanisms which contribute to regenerative processes, such as new synapses, that last from weeks till several months [139, 141]. So most of the recovery processes take place early after stroke and reduce during the late sub-acute period [85]. EEG studies have described that after a stroke, the cortical networks increase their excitability and become more influenced from LTP (Long Term Potentiation) which is correlated with plasticity [13]. However these mechanisms are not completely understood as they are influenced from spontaneous brain processes [41] and environmental stimuli.

New connections are born after the damage in the perilesional, contralesional and subcortical regions resulting in the re-mapping of the sensory, motor and speech areas [139, 105]. In adults contralesional reorganizations occurs mainly in more severe lesions and is associated with decreased motor abilities [103]. Studies of both animal and adults with stroke, have revealed the paramount role of the ipsilesional Premotor Cortex after a damage in the Primary Motor Cortex (M1) [108, 147, 103]. Wu and her team [103] found in a group of 12

hemiparetic people that those who showed, in their EEG recording, increased neural connections between the lesioned M1 and the ipsilesional Premotor Cortex, had better movement in contrast to those with increased connectivity in their ipsilesional and contralesional M1. Also it is reported that an increased neural connection between the lesioned M1 and the parietal cortex acts as a maladaptive compensatory brain reorganization linked with more severe injury.

3.2. LOCATION, TIMING AND SIZE OF PERINATAL LESION

During perinatal period, the brain undergoes massive structural changes and a lesion could interfere with the processes of neurogenesis, synaptogenesis, myelination and pruning. The brain regions are at a different neurodevelopmental phase, making the outcome different depending on size, timing and location [61, 60, 137, 177] although such suggestions remain still under investigation [105].

In regard to lesion location, motor deficits usually involve subcortical lesions and non-motor deficits involve cortical lesions [75]. In 2018 Wagenaar and her colleagues [138] attempted to associate the adverse outcomes with lesion location. Although they didn't find a linkage between outcomes and lesion in the main segment of Middle Cerebral Artery (MCA), they found that an infarction of the non-main MCA branch, which supplies with blood the basal ganglia, is linked with cognitive deficits, behavioral deficits and cerebral palsy. An infarction of the cerebral peduncle is linked with cerebral palsy and epilepsy and lastly infarction of the bilateral lesions are associated with epilepsy.

Concerning lesion timing, there is an ongoing debate whether an early injury leads to better or worse outcomes. Studies have shown that early injury of the unilateral CST, before the end of the third trimester, may lead to maladaptive brain reorganization, with the contralesional healthy hemisphere taking over motor control of both hands and resulting in hemiparetic cerebral palsy affecting mainly the upper limb [161]. Also unlike childhood stroke, perinatal stroke has been

related with deterioration of cognitive abilities in follow-up tests [101, 48]. There are some non-linear models such as the one that proposes that a stroke in the middle childhood has more favorable outcomes than in earlier and older childhood [92]. In contrast Westmacott [101] reported that, in case of cortical lesion, the period between 1 month and 5 years of age are the most vulnerable for cognition while in case of subcortical lesion the perinatal period is the most vulnerable.

Lastly regarding lesion size, studies show that cognitive impairment, particularly attention and executive function deficits, is associated with a severe lesion which does not leave the cortex unaffected and is accompanied with epilepsy [75, 177, 18].

3.3. NEURAL PLASTICITY OR NEURAL VULNERABILITY

The brain of infants and young children reacts differently to an injury in comparison with the brain of older children and adults. According to neural plasticity theory (Kennard principle) which was based firstly on Broca's ideas about the powerfulness of neural plasticity following an early injury, and later on the work of Margaret Kennard in monkeys [9, 161], proposes that the immature brain is more malleable, more capable of brain reorganization and functional recovery, as usually seen in language [36, 110, 177]. In contrast, the theory of neural vulnerability points out the susceptibility of the young brain to an injury as it still develops, resulting in negative after-effects such as maladaptive contralesional motor reorganization and later emerging cognitive deficits [61, 60, 161, 89].

3.3.1. SENSORIMOTOR PLASTICITY

Researchers have described a maladaptive motor reorganization in the contralesional hemisphere of infants who have damaged their Corticospinal Tract

(CST) after PAIS, which is related with impairment of their hand function. CST comprises the neural pathway from the Primary Motor Cortex towards structures of the brain stem that controls voluntary movement of the opposite side of the body, mainly the trunk and the extremities [89]. By the sixth-eighth month of gestation, CST axonal projections have made their synapses in the spinal cord with both hemispheres sending at the same time ipsilateral and contralateral projections [32, 161]. As neurodevelopment continues, pruning makes the brain fine-tuned based on the activity-dependent conflict between cells axons and eventually, by the end of the third postnatal trimester, each brain hemisphere becomes dominant for the opposite body movement. In case of lesion during the first 9 months, the contralesional hemisphere takes control of both sides of the body leading to problems with hand function such as mirror movement due to the “crowding effect” although this negative after-effect is not always the case [73].

Related to sensory reorganization, a damage in the Somatosensory Cortex probably will not conclude to structural and functional brain reorganization. An early lesion of the ascending thalamo-cortical axons will force these axons to make a detour around the lesion and synapse normally with the Somatosensory Cortex [161]. This is due to the fact that even though during the beginning of the third trimester of gestation the somatosensory axons have synapse with the contralateral cortex, this process continues also postnatally with the area presenting a degree of early specificity unlike the CST [64].

Motor and sensory abilities are inter-correlated, sub-serving one another giving rise to the Sensorimotor system [150]. For example proprioception have an important role in movement control [166]. Thus the maintenance of somatosensory function ipsilesional can result in a dissociation of sensory and motor functions (in case the last has been reorganized in the contralesional hemisphere) causing further motor problems [15]. However, some scientists proposed that this dissociation may be an advantage for sensory and motor functions as the lesioned hemisphere cannot serve both functions effectively [117].

3.3.2. VISUAL PLASTICITY

The increased ability of the young brain to reorganize and recover after an early lesion in the Primary Visual Cortex (V1) has been under debate due to opposite results. Some human and animal studies have reported the preservation of visual function after an early lesion in V1 due to increased brain plasticity and have compared their data to other studies which showed that a lesion during adulthood can result in cortical blindness [149]. In an animal research, Warner [151] and his colleagues found that after an early injury of V1, the level of pruning was at a lesser extent than in the control healthy group. In contrast other studies have observed that children with PAIS who have experienced cortical/cerebral visual impairment (damage in cortical and/or subcortical visual pathway) demonstrate various problems with their vision such as reduced visual acuity, impairment with their visual field [65], visual processing and attention [16].

3.3.3. LANGUAGE PLASTICITY

Language reorganization after an early lesion shows enormous effectiveness as speech in the immature brain is not yet lateralized to the left-hemisphere with regions such as uncinate fasciculus, that belongs to the ventral speech pathway, not being fully developed [4]. Thus language will grow to be supported by a more wide network.

The brain is able to reorganize language in the ipsilesional hemisphere [163], in the contralesional hemisphere [153] or bilaterally, depending presumably on factors such as lesion severity and location. In 2010 Raja and her colleagues [125] found that a bilateral activation, in children with left perinatal stroke, was connected with better language outcome. In comparison in 2019 by Francois and his colleagues [84] found that 4 year old children with PAIS, who have injured

their left frontal speech regions, activated their right symmetrical speech areas and showed better speech abilities.

3.3.4. COGNITIVE PLASTICITY

Regarding cognition, an early lesion could have deleterious effects on the structural and functional areas that mature later, such as the PFC along with its wide network [63]. In 2000 Chapman and McKinnon [17] demonstrated that an early subcortical injury disturbs the cortical and white matter that develops in the next stage. Thus an early lesion may result in deficits of the Higher Cognitive Function, such as of the domain of general intellectual abilities, implicating an early cognitive vulnerability [60, 61, 20, 101].

4. PERINATAL ARTERIAL ISCHEMIC STROKE

4.1. OVERVIEW

According to American Heart Association [75] perinatal and childhood stroke is a clinical syndrome, injuring the brain. It is close related to long-term disability [134, 62] with motor and non-motor consequences. It occurs in 3 to 25 per 100.000 children while the risk increases for neonates occurring in 1 per 4000 newborns in developed countries [75].

Perinatal Stroke can happen from the 20th gestation week till 28 days after birth with the newborns showing the greatest risk [23, 75]. Based on the onset of the symptoms it can be categorized, as acute or presumed stroke with approximately 50% rate each. In acute perinatal stroke the symptoms appear within 3 days after birth while in presumed perinatal stroke they appear after the first postnatal month and it is presumed that it was due to perinatal stroke. Also it can be categorized according to the type of the stroke as ischemic or hemorrhagic. Ischemic can involve either an arterial or venous infarct due to cerebral sinovenous thrombosis (CSVT) or cortical vein thrombosis. All types of Perinatal Stroke cause a focal brain injury which may be cortically, subcortically or mixed.

Eight in 10 times, perinatal stroke involves an arterial infarct (PAIS), with low rate of death [135]. Neonates have 6 times more chance to suffer from ischemic stroke and with males constituting the majority of the patients [75]. The rate of an infarct in the left hemisphere is approximately 80% and usually occurs in the MCA, the largest of the brain arteries, supplying with blood the frontal, parietal and temporal lobes, along with subcortical regions including the basal ganglia and internal capsule [132]. M1 or horizontal segment of the MCA branches into the lenticulostriate arteries, suppling with blood several subcortical areas such as the basal ganglia. Blockage of the main arterial segment leads to blockage of all the MCA territory while blockage of a subcortical branch will affect mainly the basal

ganglia, internal capsule and CST [138]. Also, the rate of infarct of Posterior Cerebral Artery is approximately 9% and 1% of the Anterior Cerebral Artery with less severe outcomes.

The etiology and clinical presentation of stroke in infants differ from those of older children and adults, and are still under investigation [71]. The lack of understanding of the PAIS etiology leads to absence of an appropriate treatment and prevention planning [84]. There is not a single cause of PAIS and it has been linked with various factors involving both the mother, the neonate and the placenta, while accumulation of such factors may increase eventually the chances of such injury [75, 84, 71]. Concerning the maternal risk factors, these can be the history of infertility, chorioamnionitis, oligohydramnios, premature rupture of membranes, vacuum extraction, emergency cesarean section, coagulation disorders, preeclampsia smoking and fever. The neonatal risk factors include cardiac lesions, thrombophilia, coagulation disorders, infection, trauma, hypoglycemia, and asphyxia. Multiple risk factors can co-exist in both the mother and neonate, for example increased maternal coagulation measures and decreased neonatal coagulation measures before or after the birth. Lastly, a thrombus can be created inside the placenta, then travel as an embolus inside the arteries of the neonate and potentially causing an infarction .

The symptoms after Perinatal Stroke are seizures, apnea, chewing or bicycling movement, tone changes and difficulties with feeding [23, 76]. Particularly in the acute PAIS, 70%-90% of the neonates will suffer from focal motor seizures affecting one limb during the next 12 hours [75, 23]. Two other studies with similar results found that 41.9-46% of the individuals presented hypotonia and 7%- 25.8% had apnea [1, 79]. However these symptoms can often go unnoticed. For example neonatal seizures are more subtle and shorter than an adult convulsing seizure. A child with presumed PAIS shows later a delayed motor and cognitive development, epilepsy, asymmetric motor function, or early handedness.

4.2. OUTCOMES

PAIS damages the immature brain leading to long-term disabilities with motor and non-motor deficits such as cognitive, behavioral, visuospatial, epilepsy [75, 23, 138]. Mortality is less than 10%. A study in 2007 [3] found that 68% of the 111 children with acute and presumed perinatal stroke, developed cerebral palsy while 59% of these patients were suffering from cognitive or speech deficits and 47% from epilepsy. The type of deficits and their severity vary depending from multiple factors such as lesion size, timing and location.

4.2.1 MOTOR DEFICITS

In presumed perinatal stroke, hemiparetic cerebral palsy may occur up to 80% [89, 161, 61]. These numbers are decreasing to 25%-50% in infants with PAIS affecting mainly the hand function and in lesser extent the leg. These motor deficits are caused by the infarction of the MCA which later damages the cerebral cortex, CST, basal ganglia, posterior limb of the internal capsule, and cerebral peduncles [138]. Neuroimaging techniques, such as MRI, have detected an increase of the cerebrospinal fluid, a decrease of the gray but mostly of the white matter in hemiplegic children [105, 146].

The motor symptoms such as weakness, spasticity, orthopedic difficulties, begin to be distinct from the first year as the child fails to reach on time the motor milestones, such as reaching or turn its head towards objects. With further development more motor deficits start to present such as impairment of fine motor skills and apraxia [88, 6].

4.2.2. COGNITIVE DEFICITS

Studying of the consequences in cognitive abilities can be more challenging than the consequences in motor abilities as the first present later in the course of child development [23]. Cognitive impairment after perinatal stroke is even less studied than after pediatric stroke. Most studies show an impairment of the children's intellectual, attention, inhibition, processing speed, learning and memory compared to typical children [20, 157, 18, 12] and a study in 2016 reported that their IQ fell in the low normal range [18].

Epidemiology is not that clear with studies reporting opposite results about the frequency and the commonness of the possibility of negative cognitive outcomes [19] although researchers mention that these can reach 30 to 69% in patients with PAIS [137, 23]. An older research reported that 75% of children with PAIS and pediatric stroke appeared with continuous cognitive deficits 2 years after the incidence [140].

Regarding the course of these deficits, there is still disagreement due to opposite findings whether they remain steady over time [81, 20] or they worsen as they brain matures [101, 48] especially in the case of co-existing epilepsy [81]. Grunt and his colleagues [48] found that approximately one third of their subjects with PAIS developed cerebral palsy and intellectual impairment after 2 years of birth. Also several longitudinal studies have presented data which indicate a decrease in IQ level as these children entered school [51, 102].

Impairment severity is influenced by the size of the damage, with cortical lesions being associated more with negative cognitive, language, behavioral outcome and seizures. Prognosis is even worse if the lesion is both in cortical and subcortical regions [75, 177, 20, 101]. However it has been proposed by others researchers that cognitive impairment in early stroke, in contrast to adult stroke, is little affected by lesion size and location [81].

These problems frequently affect the behavior of the child leading to behavioral difficulties. ADHD, for example, often accompanies individuals with PAIS [157].

Eventually such children will go to public schools, and approximately 8.8%-28% of them will need supplementary educational help [44].

4.2.3. LANGUAGE DEFICITS

Language is one of the least affected cognitive ability with exhibited high brain plasticity in infants after PAIS [58] although in 2018 Hart and his team [44] reported a 49% rate. Unlike adults and older children who developed aphasic symptoms after a lesion in the left hemisphere, infants show less severe impairment without differentiating significantly from typical children [69]. However there has been recently some scientific results which reported that perinatal stroke led to conduction aphasia [156]. Younger individuals with lesion in their left hemisphere presented subtle deficits in comprehension, phonological and syntactical tests [81] while other studies show that children with right-sided neonatal damage have language expressive problems [69]. There are not significant differences between a left and a right hemispheric damage, due to lack of language lateralization early on life.

4.2.4. VISUAL AND VISUOSPATIAL DEFICITS

There are not a lot of scientific reports on visual impairment after PAIS. It has been described that, in a similar way as in adults, a right-sided perinatal injury leads to impairment of the holistic visual perception and a left-sided to impairment of the analytical visual perception [137]. A child with PAIS in their V1 can experience several deficits from their basic sense of vision (visual acuity, lower visual field) till their more complex visuospatial function and attention. Studies, using the clock drawing, found that in contrast to adult injury, perinatal damage in the right hemisphere led to stimuli neglect from the right and left side compared to the control group [100]. However some mentioned that these deficits were not

apparent in the older age group (15-21 years) implicating the plastic ability of the brain. These deficits may have a negative effect on child's ability to learn, to move appropriately and generally on its life quality [16].

4.2.5. SOMATOSENSORY DEFICITS

Somatosensory deficits after perinatal stroke are less understood as they have been under-researched [61, 59]. According to literature they occur in 40% to 90% of the children with hemiplegic cerebral palsy, with the hand which is controlled by the lesioned hemisphere being more impaired than the other hand [146]. Most common deficits after perinatal stroke can be problems with graphesthesia (perception of the shape or number drawn on the skin without looking), stereognosis (perception of the identity of the held object without looking) , two-point discrimination, functions which are based on proprioception (perception of position) and kinaesthetsia (perception of motion) [59, 137]. More basic sensory function such as touch, pain, temperature and vibration remain to a fair degree unaffected. Dysfunction of proprioception can worsen the motor deficits such as in coordinated and grasping movements.

4.2.6. EPILEPSY

Seventy-five percent to ninety percent of PAIS neonates present seizures within 3 days after birth. Fifteen percent to fifty percent develops epilepsy [71, 77, 44] and 69% of neonates which presented seizures shortly after birth are at risk of suffering from epilepsy within 10 years. Epileptic spasms (epileptic encephalopathy) occurs in 5% to 10% of children with perinatal stroke and is correlated with refractory epilepsy and more often with neurodevelopmental delays [114]. This outcome is associated with cortical lesion [138]. Epilepsy, especially

refractory epilepsy, is related with even worse cognitive impairment than PAIS alone affecting the brain capacity for neuroplasticity and recovery [114, 18, 81].

4.3. NEUROIMAGING METHODS FOR DIAGNOSIS

Several neuroimaging methods are utilized to diagnose, classify PAIS, describing the cortical and/or subcortical damaged gray and white matter for screening, research and eventually therapeutic purposes. Although Cranial Ultrasound is a common, easy screening tool in most hospitals, it has small sensitivity especially in cases of cerebral convexity and injury of the brain stem [71, 135, 86]. Cranial Computed Tomography is also a common and cheap method, however its usage is limited due to not only low sensitivity on brain anatomy, but also to avoid exposing the young brain to X- radiation [98].

MRI is more valuable for diagnosis and confirmation of Perinatal Stroke along with Magnetic Resonance Angiography and Magnetic Resonance Venography [75] due to their higher spatial resolution of brain anatomy and sensitivity [76]. Diffused-weighted MRI is effective to find the time of the lesion and the potential white matter damage. However it is more difficult to perform them as the neonate must be put to the scanning suite and their high cost impedes most of the hospitals to be supplied with them [28].

Accumulated data described in a review in 2012 showed that the acute hypoxic-ischemic neonatal brain was 15%-30% normal in an MRI scan, whereas 40%-80% of the scans showed lesion in the basal ganglia and thalamus and 40%-60% of them showed alteration of the cortex and the white matter [176].

EEG recording is an important tool to monitor the neonate after the incidence for seizures, although its usage in hospitals is not as common as MRI [98]. Amplitude Integrated-EEG is used in intensive care settings providing constantly monitoring of the neonate’s brain function [2]. EEG is also practiced for

research purposes, as in to study the effects in brain activity after applying an interventional therapy and relate them to neurodevelopment [98].

EEG recording of neonates with PAIS have revealed early changes in their brain activity soon after birth [98]. Low and his team [111], when studying neonates with PAIS and seizures found a continuous EEG with voltage suppression along with intermittent theta outbursts on the lesioned hemisphere. EEG suppression was associated with the size of the lesion. Sleep cycling was also abnormal in most of the infants.

A more recent study of neonates with PAIS revealed an EEG difference between the affected and unaffected side, which was associated with the lesion size, gestation age, administration of AEDs (antiepileptic drugs) [98]. They also linked the EEG characteristics with cerebral palsy and cognitive impairment. A longer continuous voltage activity above the affected side and unaffected side was seen in infants with PAIS connected to cognitive impairment. The duration of a normal background in the affected hemisphere was connected with the emergence of cerebral palsy and negative cognitive outcomes. A study in 2018 [127] found a link between consistent EEG abnormalities, in children with Perinatal Stroke, and decreased language and cognitive abilities.

4.4. MOTOR AND NON-MOTOR REHABILITATION

Rehabilitation of PAIS mainly focuses on alleviating the symptoms and the adverse outcomes such as seizures, motor and cognitive impairment once they have appeared and does not focus on prevention of PAIS or its outcomes, due to lack of knowledge of its exact causes and mechanisms. Management of adult and child stroke is providing a basis to create an intervention for neonates who have sustained PAIS, although some of the major differences which influences the developing of such program is the fact that an infant must acquire skills and knowledge that did not have before [23].

During the last decade, various motor interventions have been developed and children with perinatal stroke and cerebral palsy have been the major contributors [23]. Motor therapeutic strategies are relying their positive effects on the principle of brain plasticity and leading the latter to advantageous results [60].

“GAME” (Goals, Activity, Motor Enrichment) is an example of motor intervention with studies revealing its positive effects on motor development and cerebral palsy rehabilitation [75]. Baby constraint-induced movement therapy, bimanual therapy, baby massage, and non-invasive brain stimulus are also applied for motor recovery focusing mainly on hands function [23, 75].

Studies have demonstrated that non-invasive brain stimulus such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) could “boost” the ipsilesional hemisphere and inhibit the maladaptive reorganization in the contralesional hemisphere. Although the advantages of these interventions are not confirmed [60].

Cognitive rehabilitation programs particularly for infants and children with PAIS remain underdeveloped. However, when entering school, additional education should be provided to those children with the most difficulties [23]. Concerning language, an early speech rehabilitation must be given to those with language difficulties.

Lastly, regarding epilepsy, early presentation of seizures can be treated with AEDs. However seizures may first occur years after the incidence and thus regular EEG monitoring is required as epilepsy is associated, as mentioned above, with adverse outcomes. In case of refractory epilepsy, a surgical operation to remove the area from which seizures are emerging, can have therapeutic results, especially if it is performed in the beginning of seizure’s emergence.

5. NEUROIMAGING OF SYNAPTOGENESIS

5.1. OVERVIEW

Several scientific methods have been used in the past to investigate neuroplasticity. It was first studied in animals using invasive techniques e.g. invasive EEG [178]. Later on, non-invasive neuroimaging techniques, such as fMRI and Transcranial Magnetic Resonance were recruited and made advances in the understanding of neuroplasticity in humans. During the last years there has been an increasing scientific interest in EEG, a non-invasive neuroimaging method with better temporal resolution (milliseconds) than fMRI, less expensive and more applicable to infants and young children.

EEG measures the oscillatory activity derived from the summed output of the excitatory and inhibitory neurons from the surface of the cortex [31]. Its traditional use has been to study the epileptic brain activity [119] but recent progress in the knowledge of EEG bands [delta (0.5-3 Hz), theta (3-8 Hz), alpha (8-12 Hz), beta (13-30 Hz), gamma (30 and higher Hz)]. Their association with different psychological functions led many scientists to employ it for the investigation of neuroplasticity [178]. However, there is still a lot of debate, due to inconsistent data, about the specific role of EEG bands in different psychological functions. One etiology is that EEG bands may demonstrate multiple cognitive functions [29].

5.2. EEG USE IN INFANTS

EEG recording, is employed in the intensive care unit for infants who are at risk for early brain injury [170]. Its purpose is to find epileptic activity or brain injury and evaluate the development and maturation of the brain. According to literature, the earliest time for an EEG recording of a newborn is 6 hours after

delivery or 3 hours for newborns who are at-risk [48]. Finn and his colleagues in 2019 [25] performed EEG recording and QEEG analysis on newborns only a few minutes after birth and discussed the significance of an early view on the infant's brain activity in order to identify as soon as possible those with brain injury.

In adults, EEG and quantitative analysis is often employed to keep track the brain functional alteration after the stroke and during recovery and therapy, providing valuable information in order to avoid structural and/or functional compensation and also maladaptive plasticity [113] In Chapter 4 the EEG characteristics of PAIS were described.

5.2.1. THE DEVELOPMENT OF EEG IN INFANTS AND CHILDREN

The borders of the various EEG bands are different between adults and children/ infants with the borders of the latter lying lower than the borders of the former [155]. EEG reactivity in an outward or inward stimulus, refers to changes in frequency, continuity, amplitude, and sleep/wake cycles. A lack of EEG reactivity in preterm neonates is typically due to pathology of connection between thalamus and cortex.

The background activity of a term newborn is synchronous (EEG elements appear with no more than 1.5 seconds difference between the 2 hemispheres) and symmetrical, except for some minutes when switch from active to quiet sleep [78]. Periodic sharp waves, in a term and preterm baby are not unusual and they don't translate immediately to brain pathology [27]. The background frequencies of an infant is slower of an adult with delta and theta bands dominating. With age this typical cortical slowing starts to disappear. By 2 months of age, infants have developed a posterior dominant rhythm (PDR) at 3-4 Hz which is the predecessor of the alpha rhythm and around 3 years of age it reaches 8 Hz. A centrally prevailing μu rhythm starts to appear between the first and second year of life, with beta-band frequencies also appearing during that period.

The EEG difference between the awake state and drowsiness is when the background activity decreases 1 or 2 Hz with an EEG activity dominating in the fronto-central area. Regarding sleep EEG recording, sleep/wake cycles begin to differentiate from each other after 31 weeks of conceptual age (CA) and specialists can begin to divide it in active or quiet sleep by 37 and 40 weeks CA. By 2 or 3 months of age, asynchronous sleep spindles start to appear. Afterwards they start to become synchronous. By 2 and 5 months V-waves and K-complexes begin to appear with the former locating in the fronto-central or central regions. Active or REM sleep, which comprise the 50% of the total sleep (active and quiet together) in neonates, starts to decrease and around 12 and 24 months of age it has dropped to 30% reaching eventually the adult level of 20% [27, 78].

5.3. DIFFERENT EEG BANDS AND NEUROPLASTICITY

The strategies employed for the study of neuroplasticity concern 2 different techniques. Numerous studies suggest that during sleep, slow waves activity, such as theta and delta activity, indicate plastic events and memory consolidation [169, 178, 131]. During wakefulness, neuroplastic events, are usually hidden by irrelevant activity and to this day awake neuroplasticity is an ongoing investigation.

In 2015, Assenza and Di Lazzaro [178] proposed that awake delta activity is associated with neuroplasticity. However increased delta activity (cortical slowing) in the awake brain is mainly considered a brain pathology [123] while ongoing post-stroke low frequencies are connected with worse outcome [26]. A more recent study with typical and preterm infants used EEG beta-1 (13-18 Hz) power as indication of synaptogenesis [21] and it will be discussed further below.

5.3.1. BETA-BAND AND FUNCTIONS

Hans Berger (1873-1941), a German psychiatrist and inventor of EEG (1924), was the first scientist who spoke about the beta waves and proposed that these waves are responsible for “mental activity” [66]. In the beginning, any frequency higher than 13 Hz was considered beta waves with gamma-band being described during the 1980’s.

In general, beta-band is one of the widest band and the most controversial, associated with a number of brain functions [29]. It is often divided into two bands based on brain site and reactivity to stimuli; Low-Beta Waves or Beta 1 (13-21 Hz) and High- Beta Waves or Beta 2 (21-30 Hz) [66].

Although it is widespread, it exists mainly frontally related with higher cognitive functions such as stimulus assessment and decision making and centrally related with sensorimotor functions [67]. When it dominates the person is awake and attentive or stressed or with opened eyes [112]. Hypnotics and sedative drugs (barbiturates and benzodiazepines) can lead to excess of beta-band frequencies and to increasment of its usual low amplitude [128].

Dominance of beta-band activity in the motor cortex, during resting state, is considered to represent the “idling rhythm” of the motor function and is associated with the preservation of the typical state of the sensorimotor cortex, assisting the generation of the next movement [31]. During unilateral movement, beta-band activity is suppressed in both hemispheres (Movement-Related Beta Desynchronization) and is restored in the contralateral hemisphere (Post-Movement Beta Rebound) once the movement is seized,. These mechanisms represent the cortical excitation during movement and inhibition at motor rest. Also, its activity it’s considered the “pacemaker” of GABA-ergic interneurons which have a crucial role in neuroplasticity as was described in Chapter 2.

Pharmacological studies in animals and humans have revealed the link of beta-band with GABA [31]. When GABA-A receptors blockers were given in-vitro in animal slices, beta activity seemed to decrease. A similar phenomenon was seen

in humans studies, where administration of GABA agonists (diazepam) or GABA reuptake inhibitor (tiagabine) increased resting beta power.

However the association of beta frequency with neuroplasticity is not straightforward with studies indicating it's potential positive role in neuroplasticity while others suggesting its negative role in that process. The consideration of beta activity as a negative sign of brain plasticity comes from studies of stroke [26], Parkinson Disease (PD) [148] and aging [97]. It was demonstrated that higher beta oscillations are associated with worse motor recovery after stroke, with the duration of PD and aging. However, in the literature, there are studies which propose a different etiology for the previous results and others that demonstrate the possible positive role of beta-band activity in neuroplasticity.

Firstly, a study in 2014 [93] found that beta power in PD patients was increased due to L-Dopa which is a standard medications in this disease. Another study which described the elevated beta power in PD found also that, after movement practice, frontal resting beta power was increased in healthy but not in PD patients suggesting abnormal cortical plasticity [148]. Second, regarding aging, it has been described that the cognitive functions on the elder brain are managed by hippocampal tonic inhibition and reducing hyperactivity in hippocampus may alleviate cognitive impairments in elders with MCI [83] and therefore suggesting that the elevated beta power in elders acts as a compensation factor in the aging brain. A 3-year long study on aging found that relative parietal beta-1 power could predict the advancement of MCI to Alzheimer (AD) with individuals who eventually developed AD demonstrating less baseline beta-1 power in the parietal region and it's consistent with previous studies which showed the decrease of fast EEG bands (alpha, beta) and increase in slow EEG bands (theta, delta) in AD patients [107]. Thirdly, Hiu and his colleagues [30] showed the dual role of GABA in plasticity after stroke with tonic (extrasynaptic) GABA transmitting being associated with functional impairment whereas phasic (synaptic) GABA transmitting being associated with functional recovery.

As it was mentioned briefly above, a recent study proposed a more straightforward association of beta power with neuroplasticity, particularly with synaptogenesis [21]. This study was based on an older study [90] which showed that preterm infants had elevated absolute beta power during 33 and 36 months taking also into account that 34 weeks of gestation is proposed as the time when synaptogenesis enters an increasing phase [21]. What Chegodaev as his team found was that 5-months but not 10-months preterm infants had lower absolute beta-1 power than the corresponding typical group, indicating physiological differences in brain maturation and particularly in the process of synaptogenesis with preterm children showing reduced synaptic growth [91].

Therefore more investigation is needed to establish how is beta-band connected with neuroplastic events in the brain.

METHOD

1. PARTICIPANTS

50 term infants and toddlers from Russia were recruited for the study in the city of Yekaterinburg in Ural region. The participation of these children was on the basis of their parents will, who volunteered to join the study. From the total 50 participants 32 were male (64%) and 18 were female (36%). Their age ranged from 4,3 till 25,7 months. 40 of these participants were typical and 10 had sustained PAIS. From the 40 typical children, 23 (57,5%) were male and 17 (42,5%) were female. From the 10 PAIS children, 9 (90%) were male and 1 (10%) was female. The overepresentation of male PAIS participants was in accordance with literature which states that mostly male infants suffer from perinatal stroke.

All of the PAIS children, according to MRI records, had sustained a mild subcortical lesion in the basin of the brain, in the MCA. In 5 of them, the stroke was in the Left Hemisphere and in 2 of them, in the Right Hemisphere. The participants matched socio-economic status.

Regarding the group making, the participants were first divided into 2 groups, typical group (TG) and PAIS group (PG), based on the principle if they had sustained PAIS or not . Secondly within these 2 groups 3 age subgroups were established according to their age; 5months, 10months and 24months. Within these three subgroups, the age of the participants varied approximately 1,5 month from the designated age of the subgroup. Due to lack of many children especially those with PAIS, several of them were placed in more than one group as they were re-examined. Specifically, from the TG 11 children were put into 2 age groups. Four children from the PG were placed into all 3 subgroups while 3 others into 2 subgroups. However the subgroups were treated as being independent and not dependent. So the volume and gender characteristics of each subgroup were as follows; 5months N_{TG}=19 (M=11, F=8), 5months N_{PG}=7 (M=5, F=2), 10months

N_{TG}=22 (M=14, F=8), N_{PG}=8 (M=8) and 24months N_{TG}=8 (M=4, F=4), N_{PG}=5 (M=4, F=1).

2. MATERIALS

Firstly, Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III; Bayley, 2006) [15] was chosen for the evaluation of the participants developmental functioning in cognition, language and movement. Secondly, the absolute beta-1 power was measured during EEG recording (128 channels) of the participant's background activity. The EEG information was analyzed with NestStation 4.6.3. software.

2.1 BAYLEY-III

Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) [7] is a well-recognized instrument which evaluates the developmental functioning of individuals from birth till 42 months and is administered to each child separately. It is constituted by 5 scales representing different developmental domains; cognitive, language, motor, social- emotional and adaptive behavior. Its aim is to detect potential developmental delays and establish an appropriate intervention based on the child's strengths and weaknesses [96].

In this particular study, only the first 3 scales were used, as the last 2 scales were considered irrelevant for the experimental purpose.

2.1.1. RELIABILITY AND VALIDITY

Bayley-III is the revised edition from the previous Bayley Scales of Infant and Toddler Development, Second Edition (Bayley-II, 1993) based on the need to be up to date with the current scientific findings, more detailed and precise about

child development. Such an example is the split between the Cognitive and Language Scale and with Motor Scale assessing separately Fine and Gross Movement in comparison to Bayley-II which provided two domains; Mental Development Index and Psychomotor Index.

The normative data are from US participants which were stratified on demographic characteristics such as age, sex, parent education level, and geographic location. In order to succeed better representation of children with different health status, the instrument included almost 10% of children who were diagnosed with a particular syndrome or disorder such as Down syndrome, cerebral palsy, pervasive developmental disorder, premature, specific language impairment, prenatal alcohol exposure.

In order to follow the fast child development accurately, the data which were collected by infants aged from 1 month till 6 months had one-month-gap between them, infants from 6 months and 12 months had two-month-gap, from 12 months till 30 months had three-month-gap and from 30 and 42 months had six-month-gap.

The reliability of the particular instrument was established based on tests that measure internal consistency, inter-rater agreement, and test–retest stability. Also its validity was confirmed by investigating the correlation between the different subtests, assessing via factor analysis its internal structure and establishing its connection with different measures including Wechsler Preschool and Primary Scales of Intelligence (Wechsler; Preschool Language Scale – Fourth edition, 2002).

2.1.2. ADMINISTRATION AND SCORING

Its administration and scoring by the well trained examiner is easy as it has clear-cut instructions, permitting the examiner to help the child to overcome its shyness, making it more relaxed and collaborative (for example by starting first

with play, gentle speech) and accepts collaboration with the parent who can prompt the child to respond appropriately to the subtest. The child sits on the chair or its caregiver's lap in order to achieve good body and head posture. Also the tool is more flexible at scoring when it assesses a child with disabilities and performs a "corrected age" in case of prematurity.

The Item which signals the starting point is the one that designates the child's chronological age or corrected age. The Items are administered with increasingly difficulty (although the examiner can choose to administer together Items which are more inter-related) and administration ends when the child scores three zeros in a row.

The completed tasks along with the uncompleted ones which are below the child's starting point are summed and give a Raw Score which later can be turned to Scaled and Composite Score with a mean score of 10 and 100 and a standard deviation of 3 and 15 respectively. Growth Score evaluates the cognitive, language etc growth level. Also it provides a percentile rank from 1 to 99 (mean=50) based on the standardization sample. These scores allow the examiner to track the child's developmental level as it grows older, to compare the different domains of the same child and with the scores of other children of the same age, providing a full picture of its intelligence (Cognitive Scale), future academic skills (Language Scale).

As the tool has not yet been standardized for a Russian population, only the Raw Scores was decided to be used.

2.1.2. COGNITIVE SCALE

For the making of Cognitive Scale, it was used up to date information about the child cognitive development, which came from studies of information processing, processing speed, problem-solving, and play. It comprises of 91 Items

in which the child engages without the need to speak and are especially designed to attract the child's interest according to its age.

For the evaluation of the child's information processing, were included Items which measured cognitive functions such as novelty preference, attention, habituation, conceptual reasoning, and memory. Processing speed (duration of task completion) was assessed via Items that measured child's attention and habituation, ability to finish a puzzle or pegboard. Problem-solving had Items which demanded reasoning, memory and information synthesis such as Item 43 in which the child should collect a desired object from behind a semitransparent screen. The evaluation of play included Items which prompted a playing behavior according to the child's age. For example exploring objects can attract an 4month infant while more complex playing situations (e.g. positioning a spoon inside a cup) are used to assess older children, with symbolic and pretend play being the highest-level kind of play.

2.1.3 LANGUAGE SCALE

As it was mentioned previously, the domain of Language has its own Scale on Bayley-III in contrast to Bayley-II, and is separated in Receptive Communication Subtest (RC) with 49 Items and Expressive Communication Subtest (EC) with 42 Items. It allows the assessment of the verbal and the non-verbal communication through the child's gestures, gaze, joint attention and vocalization.

The RC has Items such as tolerated attention, respond to name, understood use of objects while the EC has Items including social smile, participation in play routine, use of pronouns and verbs.

Both responding to language and instigating communication are associated with learning and future development with domains such as cognitive, social-emotional and adaptive behavior influencing it. For example a good level on the

social-emotional domain may promote the bipartite communication and the development of the language. The results of this scale can stand as a base for planning an early intervention in situations where the child's has low scores.

2.1.4 MOTOR SCALE

The Motor Scale is divided in 2 different subtests; Gross Motor Subtest (GM) with 66 Items and Fine Motor Subtest (FM) with 72 Items. Gross Motor development is affected by the height and weight of the child, biomechanical features, neurological development and the physical/social/cultural environment. FM development is affected by biomechanical features, perception (e.g. visual, kinaesthetic), sensation and cognition. Also, motor development is influenced by how motivated and inquisitive is the child.

Firsly, Bayley-III tool kit of Motor Scale gives the child a plethora of typical perceptual cues and opportunities to act in various ways (e.g. walking, eating, reaching, grasping) and evaluate the ways the child responds (e.g. eye tracking an object across the midline), manipulates objects at different ages (e.g. reflexive, palmar or finger grasp) and explores the environment revealing the child's interest towards objects and people and its ability to move around (e.g. eye gaze, rolling, crawling, walking). Secondly, through sequence Items, the 3 stages transition when conquering a novel motor skill are brought out; experimentation, selection of the most adaptive movement, repetitive performance. Thirdly through the different subtests (e.g. drawing, eating, buttoning) it is revealed how the motor planning develops and how the movements become more purposeful and more self-organized as the child grows older (2-4 years old), driven by social learning. Fifth, it reveals the sensory-motor integration and the participation of kinaesthetic and visual perception in the development of movement across the ages. For example an object's texture can drive the infant to inspect the object with its fingers, proprioception and visual-motor integration can assist the ability of the child to

monitor its arm and hand positions, gain balance and postural control. Sixth, it determines the development of muscle-skeletal strength which helps the child to stand, walk, jump, run, climbing up and down stairs. Seventh, the examiner is able to determine how different skills influence each other and how the past experience influence their emergence. Eighth, the erratic movements (both appropriate and inappropriate) of the child reveal an emerging skill in which an intervention may be built.

2.2. EEG

EEG recording was employed to assess brain activity and possibly synaptogenesis in the different brain regions by measuring absolute beta-1 power (13-17 Hz) of awake infants and toddlers during resting-state or background brain activity while watching a 2-3 minutes video with underwater fishes accompanied with calming music. For the EEG recording, it was used a high-density 128-channel HydroCel Geodesic Sensor Net, Net Amps 300 amplifier at the sampling rate 1000 Hz with vertex reference and the 10-20 system electrode placement. Then the data were analyzed via the NetStation 4.6.3 software.

2.2.1. RESTING-STATE EEG

EEG is a major non-invasive neuroimaging method, used to measure the activity of the subjacent brain neurons in order to investigate the typical state of the brain, to find any abnormalities or neurological diseases and also to form interventions and therapeutic planning for disorders such as autism, attention disorders, language delay, learning difficulties [159]. It provides high temporal resolution as it can record brain activity from milliseconds to seconds.

This method has been used to investigate the functional organization of the brain in various diseases including epilepsy, schizophrenia, Alzhemeir’s disease, multiple sclerosis, Parkinson’s disease or to study aging and gender differences.

Contemporary studies, have found that recording awake brain activity during its resting-state where no task is executed, can give valuable information regarding the spontaneous brain activity and revealing the basic brain state [95]. Moreover according to literature resting-state represents the functional connectivity of the different brain areas and the different networks and is associated with the activity of the resting state networks such as the “default mode network” [143].

Brain’s resting-state can be recorded during eyes closed and eyes open. With eyes closed is more difficult to maintain, between the subjects, a standard baseline of thought influencing the collection of comparable data, especially if they are infants or children who are more difficult to instruct. Also during eyes closed condition it is easier to succumb to drowsiness. Usually for the eyes open condition, participants are siting in close proximity to a screen staring to a background setting.

2.2.2 QEEG

Quantitative EEG (QEEG) analysis or “brain mapping” has the benefit of a more fast, detailed and objective brain examination as it has more electrodes attached on its head-cap (128 electrodes) and the analysis of the collected data is via computer programs such as NetStation, offering data that are reproducible for research purposes, whereas analysis of a simple EEG recording is depended mostly on the subjective visual examination where brain functional information can be masked. The breaking down of the total EEG power is attained via algorithms such as Fourier transformation (spectral analysis method) [155].

QEEG offers information about the sleep cycles of the infant, its brain functional maturation, the normal frequencies or bands characteristics associating them with different cognitive aspects, which brain regions are participating in a certain activity, a potential functional disorder and the functional changes after an intervention (e.g. neurofeedback, medication, behavioral intervention).

2.2.3. NETSTATION 4.6.3. SOFTWARE

As described in the manual, “NetStation is a complete software package for working with electroencephalography (EEG) and event-related potential (ERP) data” [136]. Firstly, before analyzing the data of the resting-state activity of infants and toddlers, a 0.5 Hz high-pass filter and a 40 Hz low-pass filter was applied in order to collect only the most meaningful brain activity. Then, a collection by marking 2-seconds epochs/segments is performed, in which the individual was successfully watching the screen without crying or moving, with the help of the time-locked to the EEG video which recorded the child during the whole process. After the epochs/segments selection, a segmentation is performed which “crops” the selected segments from the non-selected. Approximately 10-15 segments and almost 20-30 seconds were collected for the data analysis.

After the segmentation, an artifact-checking was performed. The 125, 126, 127, 128 and 17 electrodes were manually removed from every segment as they are sensible to facial and eye muscle movement artifacts. Electrodes which were placed wrong, or moved by the child, were also removed. Then a Bad Channel Replacement is performed, followed by Reference Copy, Base Line Correction and finishing with Flattening.

Moreover a Fast Fourier Transformation (FFT-spectral analysis) was performed using a Hann window, estimating the power spectral density and the absolute power of the different EEG-bands, focusing on the absolute beta-1 power.

Lastly, the results of the FFT and the Hann window were processed on Microsoft Excel, creating tables with each EEG band in each brain area.

3. PROCEDURE

The children were recruited by the Ural Federal University (Urfu) in the Lab of Brain and Neurocognitive Development, with their parents volunteering for

them to participate, during the time period of 2015-2019. Each child visited the lab, where specialists administered the Bayley-III test and performed EEG recording. The whole process would be completed in a day, although in certain cases (e.g. the child was tired to continue) it was split in 2 days. The caregiver was informed in a prior day about the process of the tools, signed an informed concent and were given instructions which he/she should follow during that time.

Firstly, the caregiver (usually the mother) and the child would arrive during morning hours or early afternoon (from 9 am till 3 pm). Right afterwards they would sit next to the table where Bayley-III test would be administered by the specialist. The child would sit on its caregiver's lap or if it was old enough on its own chair next to its caregiver. The caregiver was instructed not to help the child complete the tasks but he/she could encourage it by repeating the specialist requests and movements. Depending on the energy of the child there would be one break halfway of the test. Meanwhile, the EEG head-cap was prepared in a soapy water for several minutes by another person. The duration of the first part, depending on the child and its age, would be 1 hour or 1 and half hours.

Once the administration of Bayley's test was over, the aim of the EEG specialist and the caregiver was to distract and calm the child, usually with toys or floating bubbles, so it would wear the head-cap without much resistance. Then the caregiver would carry the child on a small dark and sound-proof room, with a computer screen, standing approximately 80 cm away from them, which would later present the stimulus (background EEG-underwater scenery). The caregiver was instructed to try and keep the child on his/her lap, comfort it so it would stop crying or try to remove the head-cap and encourage it to look at the screen with as less speech as possible. In the next room the EEG specialist was sitting, performing the recording and monitoring the child's behavior through a small video camera attached on the right of the computer screen and making sure it was actually paying attention to the screen. The duration of the stimulus would be 2-3 minutes,

however the child would continue with further different stimuli on the screen which was irrelevant for this particular study.

After the EEG recording, the parent with the child would wait inside a play-room where minutes later the parent would be debriefed regarding the whole process and some first observations about their child. More details about the results would be given once the scoring and the analysis were over.

The total stay of the caregiver and the child at the lab would approximately last to 2 and half hours.

Those children which were recruited earlier, during the period of 2016 and 2019, re-visited the lab after several months and years and re-examined two or three times.

Lastly, it is worth mentioning that Bayley-III test was revised and a Fourth Edition (Bayley-4) was published on September 2019. However the study continued to use Bayley-III as it was important that all children were tested with the same tool.

RESULTS

DESCRIPTIVE DATA

Both groups were divided into 3 different age subgroups; 5months, 10months and 24months. The absolute beta-1 power was calculated for each different brain region in each hemisphere; Prefrontal Cortex (PFC), Premotor Cortex (PMC), Sensorimotor Cortex (SMC) Temporal Cortex (TC), Parietal Cortex (PC), Occipital Cortex (OC).

Firstly, regarding the Typical group and absolute beta-1 power (see Table 1 and 2), the mean of 5month subgroup of the total right (RH) and total left (LH) hemisphere was M=0.48 and M=0.43 respectively, the means of the 10month subgroup of the total two hemispheres were M=0.63 (RH) and M=0.63 (LH) and for the 24month subgroup they reached M=1.16 (RH) and M=0.87 (LH).

Secondly, regarding the PAIS group and absolute beta-1 power (see Table 3 and 4), the mean of the 5month subgroup reached M=0.44 (total affected hemisphere-AH) and M=0.37 (total intact hemisphere-IH), the means for the 10month subgroup were M=0.65 (total AH) and M=0.63 (total IH) and for the 24month subgroup they were M=0.76 (total AH) and M=0.72 (total IH).

Based on the descriptive data for each brain region in the hemispheres, it is observable a gradual age-wise increase of absolute beta-1 power of the Typical and PAIS groups. Although this trend is most pronounced in the Typical group and particularly in its 24month subgroup and in lesser extend between the 5month and 10month subgroups. The RH has slight higher level of absolute beta-1 power than the LH. The regions of PFC and TC appear to have higher level of absolute beta-1 power across the age groups with the right PFC of the 24month subgroup followed by the PMC of the same age, reaching the highest overall level for both the Typical and PAIS group.

The level of absolute beta-1 power appears to be slight lesser in the PAIS group in comparison with the typical group especially in the left PFC and PMC of the 24month subgroup showing the biggest inter-group difference. Also the gradual increase seen in the Typical group exists in lesser extend in the PAIS group while in some regions an opposite trend is observed. Particularly in the affected PFC between the 10month and 24month subgroups the drop is from 0.91 to 0.69. There are also several other smaller drops. Between the regions, TC and OC followed by the PFC have the highest level of absolute beta-1 power with the affected TC and OC of the 24month group showing the greatest size.

The standard deviation (SD) of both groups was similar and at low levels indicating that the subjects didn't diverge much from the mean and remained all at similar values.

Table 1

Descriptive information for Absolute beta-1 power in the Typical Group, Right Hemisphere

Sub-groups		PFC	PMC	SMC	PC	TC	OC
5 months	Mean	0.74	0.46	0.32	0.27	0.6	0.49
	SD	0.09	0.04	0.04	0.02	0.07	0.05
10 months	Mean	0.68	0.55	0.48	0.47	0.85	0.75
	SD	0.05	0.05	0.05	0.04	0.07	0.08
24 months	Mean	1.58	1.23	0.9	0.57	1.28	0.9
	SD	0.28	0.37	0.24	0.08	0.23	0.19

Table 2

Descriptive information for Absolute beta-1 power in the Typical Group, Left Hemisphere

Sub-groups		PFC	PMC	SMC	PC	TC	OC
5 months	Mean	0.56	0.42	0.33	0.25	0.6	0.43
	SD	0.06	0.06	0.04	0.02	0.06	0.03
10 months	Mean	0.68	0.6	0.52	0.46	0.83	0.7
	SD	0.06	0.06	0.08	0.05	0.07	0.04
24 months	Mean	1.3	0.82	0.72	0.51	0.93	0.74
	SD	0.18	0.15	0.14	0.09	0.13	0.12

Table 3

Descriptive information for Absolute beta-1 power in the PAIS group, Affected Hemisphere

Sub-groups		PFC	PMC	SMC	PC	TC	OC
5 months	Mean	0.51	0.33	0.27	0, 3	0.53	0.69
	SD	0.12	0.06	0.03	0,04	0.13	0.19
10 months	Mean	0.91	0.55	0.49	0,41	0.81	0.73
	SD	0.32	0.21	0.19	0,07	0.28	0.13
24 months	Mean	0.69	0.59	0.45	0,68	1.07	1.08
	SD	0.12	0.13	0.02	0,2	0.27	0.33

Table 4

Descriptive information for Absolute beta-1 power in the PAIS group, Intact Hemisphere

Sub-groups		PFC	PMC	SMC	PC	TC	OC
5 months	Mean	0.43	0.28	0.23	0.29	0.48	0.53
	SD	0.06	0.05	0.04	0.04	0.06	0.09
10 months	Mean	0.77	0.61	0.47	0.46	0.74	0.71
	SD	0.21	0.2	0.1	0.07	0.15	0.08
24 months	Mean	0.74	0.55	0.49	0.6	0.98	0.93
	SD	0.1	0.1	0.08	0.13	0.24	0.24

Based on the descriptive data of Bayley Raw Scores (see Table 5, 6 and 7) it is apparent that those numbers increased with age, with the mean of FM Subtest making the biggest leap from the 5month subgroup (M_{TG}=22.1 and M_{PG}=20.5) and 10month subgroup (M_{TG}=39.73 and M_{PG}=36.63) and Cognition Scale increasing also the highest between the 10month group (M_{TG}=39,68 and M_{PG}=39.63) and 24month subgroup (M_{TG}=68 and M_{PG}=63.2).

The SD of the subjects in the typical group remained steadily at low levels (below 0) for the 5month and 10month subgroups for all the Bayley Scales, and increasing in the 24month group with the Cognitive Scale having the highest level (SD=2.88) showing that children's cognitive performance started to differentiate more as the grew older. In comparison, the PAIS group showed increased sizes of SD, especially on the Cognitive Scale of the 5month (SD=3.87) and 24month subgroups (SD=2.58), the Motor Scale of the 5month subgroup (SD_{GM}=2.43 and SD_{FM}=3.72), and the EC Subtest of the 24month subgroup (SD=3.38). Also it is apparent a fluctuation of the SD volumes between the different Scales meaning that the subjects had different performance depending on the domain and didn't have the uniformity of the typical group.

Moreover, based on the means, the Raw Scores of the different Scales between the two groups appear to be similar, almost identical with the PAIS group being consistently a “slight step” behind from the typical group. The only noteworthy differences between the groups is in the Cognitive Scale of the typical 24month subgroup where its mean reaches M=68 and the mean of the corresponding PAIS groups reaches M=63.2. In the Fine Motor Subtest, of the same subgroup, the mean of the typical group is M=58.5 and M=54.4 in the PAIS group.

Table 5

Descriptive Information for Bayley Raw Scores of the 5month subgroup

Groups		Cognitive	RC	EC	GM	FM
Typical	Mean	27.22	9	7.78	18.89	22.1
	SD	0.61	0.31	0.25	0.44	0.48
PAIS	Mean	26.5	8.67	7.33	16.17	20.5
	SD	3.87	0.76	0.8	2.43	3.72

Table 6

Descriptive Information for Bayley Raw Scores of the 10month subgroup

Groups		Cognitive	RC	EC	GM	FM
Typical	Mean	39.68	13.73	12.68	27.23	39.73
	SD	0.95	0.44	0.54	0.49	0.54
PAIS	Mean	39.63	13.5	12.88	26.75	36.63
	SD	1.29	0.5	0.61	1.32	2.43

Table 7

Descriptive Information for Bayley Raw Scores of the 24month subgroup

Groups		Cognitive	RC	EC	GM	FM
Typical	Mean	68	29.5	24.5	42.12	58.5

Table 7 (continued)

Groups		Cognitive	RC	EC	GM	FM
	SD	2.88	1.58	1.59	1.,08	1.27
PAIS	Mean	63.2	27.8	22.2	40.2	54.4
	SD	2.58	1.5	3.38	1.24	1.6

HYPOTHESIS 1

The first hypothesis questioned whether the EEG brain activity, and specifically the level of absolute beta-1 power shows more interhemispheric asymmetry in the PAIS group in comparison with the typical group. To examine this hypothesis, a series two-tailed Mann-Whitney U tests were performed to compare the two hemispheres within the groups where each brain region was compared with the corresponding region of the opposite hemisphere. However the interhemispheric differences in both groups were not significant.

Firstly regarding the Typical 5month subgroup the U- values, the p-values and the $U_{critical}$ that indicate the differences between the RH and LH were as follows; Left (Mdn=0.56) and Right (Mdn=0.46) PFC [U= 120, p= 0.8, U_{crit}=113], Right (Mdn=0.45) and Left (Mdn= 0.38) PMC [U= 150, p= 0.37, U_{crit}= 113], Right (Mdn=0.28) and Left (Mdn= 0.27) SMC [U=167, p=0.7, U_{crit}=113], Right (Mdn= 0.29) and Left (Mdn=0.27) PC [U= 152, p=0.41, U_{crit}=113], Right (Mdn=0.53) and Left (Mdn=0.5) TC [U=175, p=0.88, U_{crit}=113], Right (Mdn= 0.48) and Left (Mdn=0.43) OC [U=150, p=0.37, U_{crit}=113].

The U- and p- values for the Typical 10month subgroup were; Right (Mdn= 0.69) and Left (Mdn= 0.68) PFC [U=242, p=0.99, U_{crit}=171], Right (Mdn= 0.54) and Left (Mdn=0.6) PMC [U=216, p=0.54, U_{crit}=171], Right (Mdn= 0.49) and Left (Mdn=0.46) SMC [U=236, p=0.89, U_{crit}=171], Right (Mdn= 0.48) and Left (Mdn= 0.4) PC [U=227, p= 0.72, U_{crit}=171], Right (Mdn= 0.89) and Left (Mdn= 0.85) TC

[U=229, p=0.77, U_{crit}=171], Right (Mdn=0.75) and Left (Mdn=0.67) OC [U=238, p= 0.93, U_{crit}=171].

And the U- and p-values for the Typical 24month subgroup were; Right (Mdn=1.3) and Left (Mdn=1.13) PFC [U=24, p=0.42, U_{crit}=13], Right (Mdn=0.8) and Left (Mdn=0.73) PMC [U=27, p= 0.63, U_{crit}=13], Right (Mdn=0.57) and Left (Mdn=0.58) SMC [U=29, p=0.79, U_{crit}=13], Right (Mdn= 0.48) and Left (Mdn= 0.4) PC [U=19, p=0,19, U_{crit}=13], Right (Mdn=1.02) and Left (Mdn=0.82) TC [U=19, p=0.19, U_{crit}=13], Right (Mdn=0.69) and Left (Mdn=0.61) OC [U=23, p= 0.37, U_{crit}=13].

Secondly, regarding the PAIS 5month subgroup the U- and p-values which indicate the differences between the AH and the IH were as follows; Affected (Mdn= 0.44) and Intact (Mdn=0.43) PFC [U= 21, p=0.7, U_{crit}=8], Affected (Mdn= 0.3) and Intact (Mdn=0.29) PMC [U=20, p=0.61, U_{crit}=8], Affected (Mdn= 0.26) and Intact (Mdn=0.29) SMC [U=19, p=0.52, U_{crit}=8], Affected (Mdn=0.3) and Intact (Mdn=0.29) PC [U=24, p=1, U_{crit}=8], Affected (Mdn=0.36) and Intact (Mdn=0.49) TC [U=21, p=0.7, U_{crit}=8], Affected (Mdn=0.4) and Intact (Mdn=0.49) OC [U=23, p= 0.89, U_{crit}=8].

The U-values, p-values and $U_{critical}$ for the PAIS 10month subgroup were; Affected (Mdn=0.54) and Intact (Mdn=0.53) PFC [U=31, p=0.96, U_{crit}=13], Affected (Mdn=0.42) and Intact (Mdn=0.49) PMC [U=24, p=0.42, U_{crit}=13], Affected (Mdn=0.42) and Intact (Mdn=0.43) SMC [U=23, p=0.37, U_{crit}=13], Affected (Mdn=0.42) and Intact (Mdn=0.47) PC [U=28, p=0.71, U_{crit}=13], Affected (Mdn=0.57) and Intact (Mdn=0.7) TC [U=27, p= 0.63, U_{crit}=13], Affected (Mdn= 0.64) and Intact (Mdn=0.68) OC [U=30, p= 0.87, U_{crit}=13].

And the U-values, p-values and $U_{critical}$ for the PAIS 24month subgroup were; Affected (Mdn=0.62) and Intact (Mdn=0.53) PFC [U=10, p=0.67, U_{crit}=2], Affected (Mdn=0.48) and Intact (Mdn=0.49) PMC [U=11, p=0.83, U_{crit}=2], Affected (Mdn=0.46) and Intact (Mdn=0.43) SMC [U=12, p=1, U_{crit}=2], Affected (Mdn= 0.63) and Intact (Mdn=0.47) PC [U=11, p=0.83, U_{crit}=2], Affected (Mdn=

0.8) and Intact (Mdn=0.7) TC [U=12, p=0.1, U_{crit}=2], Affected (Mdn=0.94) and Intact (Mdn=0.68) OC [U=11, p=0.83, U_{crit}=2],

HYPOTHESIS 2

Based on the above results it was impossible to put to test the second hypothesis which questioned whether greater contralesional absolute beta-1 power would be associated with worse Motor Raw Scores on Bayley-III test.

HYPOTHESIS 3

The third hypothesis tries to investigate the early vulnerability of the PFC and the emergence of absolute beta-1 power differences in the PFC of the 24month Typical and PAIS groups and the emergence of differences in the Cognitive Raw Scores between the 24month Typical and PAIS groups.

In contrast from the previous group comparisons, the absolute beta-1 power of the PAIS group was now divided in RH and LH, removing those who had suffered from a right hemispheric lesion and reducing the PAIS population; 5month (N=6), 10month (N=6), 24month (N=4). A series of one-tailed Mann-Whitney U-test were conducted.

Firstly, in the 5month subgroups the Typical Right PFC (Mdn=0.56) is statistically higher than the PAIS Right PFC (Mdn= 0.46) [U=29, p=0.04, U_{crit}=30]. Secondly no difference was found in the 10month typical and PAIS subgroups regarding absolute beta-1 power in their PFC. Thirdly in the 24month subgroups, the Typical Right (Mdn=1.3) and Left PFC (Mdn=1.13) was significantly higher than the PAIS Right (Mdn=0.64) and Left PFC (Mdn=0.65) with [U=3, p=0.01, U_{crit}=8] and [U= 8, p= 0.04, U_{crit}=8] respectively.

The differences between the Cognitive Raw Scores of the Typical and PAIS groups were assessed by performing several one-tailed Mann-Whitney U-tests with

the premise that the Typical Raw Scores were significantly higher than the PAIS Raw Scores. It was found appropriate to include in this section the comparison of the Language Raw Scores (RC and EC) of the two groups. According to results the two groups did not show any statistical significant difference.

Firstly, the results of the comparison between the two 5month subgroups which were as follows; Typical (Mdn=27.5) and PAIS Cognitive Raw Scores (Mdn=25.5) [U=45.5, p=0.29, U_{crit}=28], Typical (Mdn=8.5) and PAIS RC Raw Scores (Mdn= 8) [U=41, p=0.2, U_{crit}=28], Typical (Mdn=7.5) and PAIS EC Raw Scores (Mdn= 6.5) [U=35.5, p=0.11, U_{crit}=28].

Secondly, the results for the 10month subgroups were as follows; Typical (Mdn=39) and PAIS Cognitive Raw Scores (Mdn=39) [U=84.5, p=0.44, U_{crit}=52], Typical (Mdn=13) and PAIS RC Raw Scores (Mdn=13) [U=82.5, p=0.4, U_{crit}=52], Typical (Mdn=12.5) and PAIS EC Raw Scores (Mdn=13) [U=85, p=0.45, U_{crit}=52].

And thirdly, the results for the 24month subgroups were as follows; Typical (Mdn=67) and PAIS Cognitive Raw Scores (Mdn=63) [U= 12, p= 0.13, U_{crit}=8], Typical (Mdn=28.5) and PAIS RC Raw Scores (Mdn=28) [U= 14, p= 0.25, U_{crit}=8], Typical (Mdn=23) and PAIS EC Raw Scores (Mdn=19) [U= 12, p= 0.13, U_{crit}=8].

So, the study found unilateral differences in absolute beta-1 power of the Right PFC of the Typical and PAIS 5month and 10month subgroups. It also found bilateral differences in absolute beta-1 power of PFC of the Typical and PAIS 24month subgroups. No difference was found between the Cognitive and Language Raw Scores of the two main groups.

HYPOTHESIS 4

The fourth hypothesis, acts as complementary to the third hypothesis, suggesting that absolute beta-1 power differences in PMC and SMC would be found in all the subgroups of the two main groups, along with differences in the Motor Raw Scores (FM and GM). A series of one-tailed Mann Whitney U-tests

were conducted. Also, the study found appropriate to mention in this section the comparison between the rest of the brain areas.

Firstly, in the 5month subgroups the Typical Right PMC (Mdn=0.45) and PAIS Right PMC (Mdn=0.31) approaches the critical p-value [U=33, p=0.06, U_{crit}=30] and the Typical Left PC (Mdn=0.46) is statistically higher than the PAIS Left PC (Mdn= 0.3) [U= 24, p=0.01, U_{crit}=30]. Secondly the 10month typical and PAIS subgroups were mostly equal. Thirdly in the 24month subgroups, the Typical Right SMC (Mdn=0.57) was significantly higher than the PAIS Right SMC (Mdn=0.39) [U=8, p=0.04, U_{crit}=8].

The differences between the Motor Raw Scores of the Typical and PAIS groups were assessed by performing several one-tailed Mann-Whitney U-tests with the premise that the Typical Motor Raw Scores were significantly higher than the PAIS Motor Raw Scores. No statistical significant difference was found. However in the 5month subgroup, the 10month subgroup and the 24month subgroup comparison the FM Raw Scores, GM Raw Scores and again GM Raw Scores respectively approach $p<0.05$.

Firstly, the results of the Bayley Raw Scores comparison between the two 5month subgroups which were as follows; Typical (Mdn=19) and PAIS FM Raw Scores (Mdn=16) [U=30, p=0.05, U_{crit}=28],Typical (Mdn=22) and PAIS GM Raw Scores (Mdn=16.5) [U=36.5, p=0.12, U_{crit}=28].

Secondly, the results for the 10month subgroups were as follows; Typical (Mdn=27) and PAIS FM Raw Scores (Mdn= 26) [U=69, p=0.19, U_{crit}=52],Typical (Mdn=40) and PAIS GM Raw Scores (Mdn= 36) [U=52.5, p= 0.05, U_{crit}=28].

And thirdly, the results for the 24month subgroups were as follows; Typical (Mdn=41.5) and PAIS FM Raw Scores (Mdn=41) [U= 13.5, p= 0.18, U_{crit}=52], Typical (Mdn=59) and PAIS GM Raw Scores (Mdn=55) [U= 9.5, p= 0.07, U_{crit}=8].

So, the 5months PAIS group showed lower beta-1 power in their Left PC and Right PMC and the 24month PAIS children showed lower beta-1 power in their Right SMC than the Typical children. Also no statistical significant

difference was found between the Motor Raw Scores of the Typical and PAIS groups. However in the 5month, 10month and 24month subgroups comparison, the difference in FM, GM and GM respectively, approaches $p< 0.05$.

SECONDARY ANALYSIS: AGE COMPARISON OF ABSOLUTE BETA-1 POWER

Kruskal Wallis tests were conducted to calculate the difference of the absolute beta-1 power's level between the three different subgroups. At first, in the typical group, it was detected a statistical significant difference between the 5month, 10month and 24month subgroups in all their brain areas (see Table 8 and 9).

Table 8

Kruskal Wallis test comparison between the absolute beta-1 power of the brain areas of the 5month, 10month and 24month Typical Subgroups, Right Hemisphere

Brain Areas	N	df	x^2	p-value
PFC	49	2	12.022	0.0025
PMC	49	2	7.182	0.0276
SMC	49	2	11.027	0.004
PC	49	2	18.737	0.0001
TC	49	2	10.506	0.0052
OC	49	2	8.634	0.0133

*$p<0.05$, $x^2_U= 5.991$

Table 9

Kruskal Wallis test comparison between the absolute beta-1 power of the brain areas of the 5month, 10month and 24month Typical Subgroups, Left Hemisphere

Brain Areas	N	df	x^2	p-value
PFC	49	2	15.378	0.0005
PMC	49	2	9.534	0.0085
SMC	49	2	11.986	0.0025

Table 9 (continued)

Brain Areas	N	df	x^2	p-value
PC	49	2	20.867	0
TC	49	2	9.233	0.0099
OC	49	2	17.87	0.0001

*$p<0.05$, $x^2_U= 5.991$

Then, Mann-Whitney U-tests were conducted as post-hoc test in order to find which particular subgroups were different. A Bonferroni correction was applied (0.05/18) based on the number of comparisons in a single hemisphere, adjusting the α level=0.00277. Firsly, it was detected a statistical significant difference between the 5month to the 24month subgroups in brain areas including bilateral PFC, bilateral PC, Left SMC and with Left PMC, Right SMC, and Right TC approximating $p<0.0027$ (see Table 10 and 11).

Table 10

Mann Whitney U-test comparison between the absolute beta-1 power of the brain areas of the Typical 5month and 24month subgroups, Right Hemisphere

Brain Areas/subgroup	Median	*U*-value	p-value(two-tailed)
5m PFC	0.56	19	0.002
24m PFC	1.29		
5m PMC	0.45	28	0.01
24m PMC	0.79		
5m SMC	0.28	22	0.004
24m SMC	0.57		
5m PC	0.29	5	0.0001
24m PC	0.48		
5m TC	0.53	22	0.004
24m TC	1.02		
5m OC	0.48	35	0.03
24m OC	0.68		

*p<0.0027, U_{Crit}=38

Table 11

Mann Whitney U-test comparison between the absolute beta-1 power of the brain areas of the Typical 5month and 24month subgroups, Left Hemisphere

Brain Areas/subgroup	Median	*U*-value	p-value(two-tailed)
5m PFC	0.46	9	0.0004
24m PFC	1.13		
5m PMC	0.38	25	0.007
24m PMC	0.72		
5m SMC	0.27	18	0.0022
24m SMC	0.57		
5m PC	0.27	9	0.0004
24m PC	0.39		
5m TC	0,5	27	0.009
24m TC	0.82		
5m OC	0.43	33	0.02
24m OC	0.61		

*p<0.0027, U_{Crit}=38

The comparison between the typical 5month and 10month subgroups revealed statistical significant differences in the bilateral PC and Left OC with Right OC approximating the p<0.0027 (see Table 12 and 13).

Table 12

Mann Whitney U-test comparison between the absolute beta-1 power of the brain areas of the Typical 5month and 10month subgroups, Right Hemisphere

Brain Areas/subgroup	Median	*U*-value	p-value(two-tailed)
5m PFC	0.56	203	0.87
10m PFC	0.69		

Table 12 (continued)

Brain Areas/subgroup	Median	*U*-value	p-value(two-tailed)
5m PMC	0.45	169	0.29
10m PMC	0.54		
5m SMC	0.28	122	0.02
10m SMC	0.49		
5m PC	0.29	75	0.0004
10m PC	0.48		
5m TC	0.53	121	0.02
10m TC	0.89		
5m OC	0.48	108	0.008
10m OC	0.75		

*p<0.0027, U_{Crit}=145

Table 13

Mann Whitney U-test comparison between the absolute beta-1 power of the brain areas of the Typical 5-month and 10-month subgroups, Left Hemisphere

Brain Areas/subgroup	Median	*U*-value	p-value(two-tailed)
5m PFC	0.46	154	0,15
10m PFC	0.68		
5m PMC	0.38	121	0.02
10m PMC	0,6		
5m SMC	0.7	119	0.01
10m SMC	0.46		
5m PC	0.27	54	<0.00001
10m PC	0.4		
5m TC	0.5	113	0.01
10m TC	0.85		
5m OC	0.43	48	<0.00001
10m OC	0.67		

*p<0.0027, U_{Crit}=145

When comparing the Typical 10month and 24month subgroups, the absolute beta-1 power was statistically significant different in the bilateral PFC (see Table 14 and 15). Also the difference between brain areas of these subgroups, including SMC, PC, TC, OC becomes even less sharp than the previous subgroups (5month-10month).

Table 14

Mann Whitney U-test comparison between the absolute beta-1 power of the brain areas of the Typical 10month and 24month subgroups, Right Hemisphere

Brain Areas/subgroup	Median	*U*-value	p-value(two-tailed)
10m PFC	0.69	17	0.0009
24m PFC	1.3		
10m PMC	0.54	44	0.04
24m PMC	0.8		
10m SMC	0.49	48	0.06
24m SMC	0.57		
10m PC	0.48	69	0.38
24m PC	0.48		
10m TC	0.89	55	0.12
24m TC	1.02		
10m OC	0.75	79	0.65
24m OC	0.69		

*p<0,0027, U_{Crit}=52

Table 15

Mann Whitney U-test comparison between the absolute beta-1 power of the brain areas of the Typical 10-month and 24-month subgroups, Left Hemisphere

Brain Areas/subgroup	Median	*U*-value	p-value(two-tailed)
10m PFC	0.68	18	0.001
24m PFC	1.13		
10m PMC	0.6	61	0.21

Table 15 (continued)

Brain Areas/subgroup	Median	*U*-value	p-value(two-tailed)
24m PMC	0.73		
10m SMC	0.46	49	0.07
24m SMC	0.58		
10m PC	0.4	84	0.87
24m PC	0.4		
10m TC	0.85	77	0.62
24m TC	0.82		
10m OC	0.67	79	0.68
24m OC	0.61		

*p<0,0027, U_{Crit}=52

Secondly, according to Kruskal Wallis test, only the Intact SMC was statistical significant different between the 5month, 10month and 24month PAIS subgroups (see Table 14, 15). However the areas of the Affected SMC, Intact PMC and Intact TC were approximating statistical significant difference.

Table 16

Kruskal Wallis test comparison between the absolute beta-1 power of the brain areas of the 5month, 10month and 24month PAIS Subgroups, Affected Hemisphere

	N	df	x^2	p-value
PFC	20	2	0.642	0.7254
PMC	20	2	2.332	0.3117
SMC	20	2	5.688	0.0582
PC	20	2	4.36	0.113
TC	20	2	3.471	0.1763
OC	20	2	1.64	0.44

*p<0.05, x^2_U= 5.991

Table 17

Kruskal Wallis test comparison between the absolute beta-1 power of the brain areas of the 5month, 10month and 24month PAIS Subgroups, Intact Hemisphere

	N	df	x^2	p-value
PFC	20	2	4.484	0.1062
PMC	20	2	5.497	0.064
SMC	20	2	7.64	0.0219
PC	20	2	4.906	0.0861
TC	20	2	5.597	0.0609
OC	20	2	4.288	0.1172

*$p<0.05$, $x^2_U= 5.991$

Then, Mann Whitney U-test with Bonferroni correction was conducted to determine the exact differences in the SMC; Intact 5month (Mdn= 0.28) and Intact 24month (Mdn=0.41) SMC [U= 1, p(two-tailed)= 0.009, U_{Crit}=13]. Thus the difference with the α level correction was not statistically significant.

So, in conclusion, Kruskal Wallis test showed statistical significant difference between all the brain areas of the three Typical subgroups and between the Intact SMC of the 5month and 24month PAIS subgroups. The post-hoc analysis with Bonferroni correction in the Typical 5month and 24monh subgroups found significant differences in the bilateral PFC, bilateral PC, Left SMC and with Right SMC, Right TC and Left PMC approximating the p-value. In the post-hoc analysis of the Typical 5month and 10month subgroups there were differences in the bilateral PC, left OC, and the Right OC approximated the p-value and in post-hoc analysis of the Typical 10 and 24 month subgroups the only significant difference was in the bilateral PFC. The post-hoc analysis of the PAIS group render the difference, from Kruskal Wallis test, non significant.

CONCLUSION

This study attempted not only to broaden the scientific knowledge on PAIS and on methods that would contribute to the creation of effective interventions but also to the understanding of the awake neuroplasticity and its mechanisms during neurodevelopment or after an early lesion in infants and toddlers by establishing the absolute beta-1 power as a biomarker of synaptogenesis and understand whether the young brain is more plastic or more vulnerable to early lesions.

PAIS is clinical syndrome associated with infant mortality and with long-term motor and non-motor impairment and factors such as location can determine the outcomes. The majority of the studies have associated cognitive problems with cortical lesions and motor problems with subcortical lesions. Interventions are usually developed after the appearance of the symptoms and in that way they participate to their persistence as the symptoms are not dealt with at an early stage.

The measurement of early awake neuroplasticity for the detection of brain lesions is still debated. Beta-band is regarded the pacemaker of GABA's function with the depolarizing, and possibly hyperpolarizing, GABA-ergic neurons been connected with synaptogenesis in the developing brain or after a lesion. However these scientific views remain controversial and under scientific investigation.

The sample of this study had experienced a mild subcortical PAIS occluding the MCA and affecting the basin of the brain.

The first and second hypothesis about inter-hemispheric asymmetry of absolute beta-1 power and the association of a more contralesional recording of beta-1 power with worse motor outcome, was based on previous studies relating contralesional reorganization, in perinatal and adult stroke, to motor problems. However no interhemispheric asymmetry in the PAIS group was detected. One possible explanation for this result could be the small sample of the PAIS group and the non severity of the stroke lesion.

The third and fourth hypothesis attempted to reveal the different maturational rate of synaptogeneis in different brain areas. They are based on the neurodevelopmental principle which describes that brain maturation follows a posterior to anterior course with the Primary areas, such as SMC, developing first followed by the Associative areas, such as PFC. Synaptogenesis is the main "event" during the first 2 years. This prolonged development of PFC makes it more vulnerable to early lesions while the emergence of the cognitive deficits are delayed, rendering their study more challenging. However the volume of these problems often falls to the low normal range.

Specifically, the third hypothesis anticipated to find differences, between the 24month Typical and PAIS subgroups, in their level of beta-1 power of PFC along with differences in their cognitive performance. Although the results did not follow exactly the hypothesis, the early uniltareral beta-1 atypicalities in the PFC of the affected children, which become bilateral in the second year, in addition with the appearance of certain weaknesses in the cognitive performance also in the second year, may lead to the following assumption; synaptogenesis in PFC is affected from the PAIS at an early stage but it is only in the second postnatal year, when PFC reaches its synaptogenesis peak, that the full extent of the lesion is revealed and the cognitive performance starts to become affected as well.

The fourth hypothesis anticipated to find differences between the PAIS and Typical children, in their level of beta-1 power of SMC along with differences in their motor performance, in all the subgroups. Based on the results, the affected children showed early mild motor deficits and beta-1 atypicalities, in brain areas which are directly or indirectly responsible for movement including PMC, SMC, PC and even PFC. The first two areas have a direct relation with movement with PMC preparing the movement and the SMC controlling the movement. PC is responsible, inter alia, for proprioception and navigation in space while PFC was considered from the period of Luria as the cortical ending of the motor analyzer with strong connections with the motor areas. The early development of the

Sensorimotor areas may be the reason of the early emergence of the motor weaknesses.

Several conclusions can be drown from the above four hypotheses. Firstly, the limited performance difference and the inter-hemispheric symmetry in beta-1 power could be explained from the non severe lesion and possibly from the fact that the affected areas, didn't show beta-1 atypicalities, in both hemispheres at the same time (except for PFC) which may led to a companesation by the opposite unaffected area. However it was apparent that the performance of the affected children was always one step behind from the healthy children. The motor and cognitive weaknesses could become more prominent as these children grow older. Secondly, the bilateral atypicalities of the affected children in certain areas of their brain suggest the existence of a large brain network in which a lesion can influence multiple locations within it and in both hemispheres. Thirdly, the existing motor weaknesses in all 3 PAIS groups, in comparison with the delayed and less pronounced cognitive weaknesses, may support those studies which associate motor deficits, in contrast to cognitive deficits, with subcortical lesions. Also it may support the development from Primary to Associative brain areas.

Finally, in the secondary analysis, the beta-1 power comparison between the different ages of the healthy and affected children revealed an alteration of the maturational process in the lesioned brain, as the increase of beta-1 power over the months, in the children with PAIS, is neglectful. Also a posterior to anterior trajectory of brain development is implied as it is observed a limited increase of beta-1 power in the Primary Cortices during the first year of the child's life and non between the first and second year, in comparison with an increase of beta-1 power in the PFC during the second year of life. This observation is in accordance with literature, describing that the brain development follows a posterior to anterior course and the peak of synaptogenesis in the Primary Areas is during the first half of the first postnatal year and is followed by a more gradual increase until 12 months of life and then by a gradual decrease in contrast with the Associate Areas,

such as PC and PFC, which develop later and with synaptogenesis in PFC reaching its first peak after the first year.

Overall, absolute beta-1 power and the function of GABA-ergic system might be linked with early typical and post-lesional synaptogenesis, a remark which is based firstly on the occurrence of beta-1 atypicalities in brain areas of the affected children related with movement and cognition and at the same time the existence of motor and cognitive weaknesses. Secondly the posterior to anterior increase of beta-1 power in the healthy brain, and the fact that beta-1 atypicalities in motor areas along with motor weaknesses appear first than cognitive, may imply the posterior to anterior maturation course, with synaptogenesis constituting the main “event” during the first postnatal years. However, this association may be indirect given from non-existing differences between the 10month affected and healthy even-though they show the same motor weakness. So intermediate factors may exist that the study didn’t consider or anticipate. These factors could be related with lesion differences, even small ones, the environment and/or genetics.

The early vulnerability of the PFC could be indicated from the fact that the bilateral beta-1 power PFC atypicalities emerged in the second year of the affected children, in comparison with the earlier unilateral PFC atypicalities. Further retesting of these children could reveal an increase of the cognitive deficits.

The characteristic of the young brain to be more plastic or more vulnerable could not be clearly determined. It was apparent that a mild early lesion led to mild deficits, mainly motor, placed in the low normal range. However the fact that the affected children showed altered brain maturation but not extreme performance weaknesses could imply that the brain was still able to manage with the consequences of the lesion.

The limitations of the study were at first the small sample, mainly in the PAIS group, which could influence the lack of statistical significant results in various instances during analysis. Moreover, the limited number of affected children, thwarted the creation of three subgroups which were comprised from the

same sample. Also, the lack of tracking the affected children as they grew older impeded to study whether these early beta-1 atypicalities led to further developmental deficits. Lastly, the lack of recruitment of children with more severe lesions impeded the study of the brain's reaction to a more critical injury and the generalization of the results to all the PAIS population.

Further study is required to determine with more clarity the relation of beta-1 power with synaptogenesis as their in-between association is relatively new. It is proposed the recruitment of a larger sample, with the same children constituting the different age groups. The recruitment of children with both mild and severe PAIS could give valuable information about how the young brain reacts to these two different situations, comparing it also with their performance. Also, controlling for health and social status and using multiple statuses could provide insight about how other factors might influence synaptogenesis. Lastly, making the study longitudinal, by re-testing the participants in older ages, can shed more light on the two conflicting theories about brain plasticity, assess how the brain continues to react to lesion as it matures further, focusing more on the PFC and the development of cognitive abilities.

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